

ANNALS OF INTERNAL MEDICINE

MAURICE C PINCOFFS

Editor

VOLUME 9

(OLD SERIES, VOLUME XIV)

1935 - 1936

Contents

NUMBER 1, JULY, 1935

Presidential Address	JONATHAN C MEAKINS	1
Presentation of the John Phillips Memorial Medal		12
The Thyroid Stimulating Hormone of the Anterior Pituitary Gland	LEO LOEB	13
The Present Status of Artificial Pneumothorax in the Treatment of Lobar Pneumonia	SIMON S LEOPOLD and LOUIS M LIEBERMAN	19
Aggranulocytosis	HENRY JACKSON, JR	26
Cyclical Agranulocytic Angina	D J STEPHENS and JOHN S LAWRENCE	31
The Etiology and Prevention of Anemia in Pregnancy	MAURICE B STRAUSS	38
Study of Nine Cases of Bronchomoniliasis	JOHN W FLINN, ROBERT S FLINN, and ZEBUD M FLINN	42
The Treatment of Acute Mercuric Chloride Poisoning	EDGAR HULL and LOUIS A MONTE	54
"Eventration" of the Right Diaphragm Report of a Case with Review of the Literature, Chiefly from the Standpoint of Etiology and Diagnosis	L FELDMAN, I M TRACER, and M I KAPLAN	62
Case Reports		
Instant Death in Bacterial Endocarditis Report of a Case of Mycotic Ulceration of the Conduction System	JOHN G KIDD	78
Splenic Vein Thrombosis and Its Relationship to Banti's Syndrome, with Report of a Case	HARRY D LEINOFF	85
Allergic Coryza at Menstruation from Ovarian Hormone	FRANK A RIEBEL	91
Editorials		93
Reviews		96
College News Notes		102
Excerpts from Minutes of the Meetings of the Board of Regents		107

NUMBER 2, AUGUST, 1935

The Acute Cor Pulmonale	PAUL D WHITE	115
Effect of Vibratory Stimulation on the Neutrophilic Index	JAMES C HEALY, MARION H SWEET, and FELIX P CHILLINGWORTH	123
A Study of 118 Readmissions to Oakhurst Sanatorium of Grays Harbor County, Washington	HOWARD L HULL	133
Myasthenia Gravis	WALTER M BOOTHBY	144
Recent Studies on Anti-Hormones	J B COLLIP	150
Experimental Air Embolism	JOSEPH B WOLFFE and HAROLD F ROBERTSON	162
Recent Advances in Carbohydrate Metabolism with Particular Reference to Diabetes Mellitus	C N H LONG	166
The Incidence of the Clinical Types of Syphilis in Males, in Pregnant and Non-Pregnant Females	WILLIAM C MENNINGER and JAROLD E KEMP	175
A Clinical Study of the Mild Grades of Hypothyroidism	BLANTON P SEWARD	178
Pernicious Anemia with Normal Blood Picture	CONLEY H SANFORD	189

Case Reports

- Dinitrophenol and Rapidly Developing Cataracts W W BOARDMAN 195
 Toxic Reaction to Alpha-Dinitro-Ortho-Cresol MURRAY B GORDON
 and MARK J WALLFIELD 198
 Primary Costal Osteomyelitis HAROLD R ROEHM 200

Editorial 207

Reviews 210

College News Notes 213

NUMBER 3, SEPTEMBER, 1935

- Pulmonary Fibrosis and Emphysema JAMES ALEXANDER MILLER 219
 Etiology of the Pulmonary Fibroses and Medico-Legal Aspects of Pneumokoniosis WM S McCANN 234
 Treatment of Chronic Rheumatoid Arthritis, Further Observations on the Use of Streptococcal Vaccine CHARLES W WAINRIGHT 245
 Gastric Acidity in Chronic Arthritis EDWARD F HARTUNG and OTTO STEINBROCKER 251
 Differential Diagnosis of Diseases of the Liver B B VINCENT LYON 257
 Treatment of Peripheral Vascular Disease by Means of Suction and Pressure E M LANDIS and L H HITZROT 264
 Von Gierke's Glycogen Disease LIONEL M LINDSAY, ALAN ROSS and F W WIGGLESWORTH 274
 Diverticulosis of the Large Intestine, An Evaluation of Historical and Personal Observations HAROLD C OCHSNER and J ARNOLD BARGEN 282
 Internal Myxedema Report of a Case Showing Ascites, Cardiac, Intestinal and Bladder Atony, Menorrhagia, Secondary Anemia and Associated Carotinemia ROBERTO F ESCAMILLA, H LISSER, and H CLARE SHEPARDSON 291
 Recovery from Coronary Thrombosis, Report of Eight Cases, with Particular Reference to the Recognition of the Less Severe and Atypical Types CARTER SMITH and H CLIFF SAULS 311
 Case Reports
 Pulmonary Torulosis Report of a Case ROBERT M HARDAWAY and PAUL M CRAWFORD 334
 Primary Tumors of the Heart, with Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis before Death SAMUEL A SHELBURNE 340
 Editorial 350
 Reviews 353
 College News Notes 356

NUMBER 4, OCTOBER, 1935

- Further Studies on the Thymus and Pineal Glands L G ROWNTREE, J H CLARK, A STEINBERG, A M HANSON, N H EINHORN and W A SHANNON 359
 Artificial Pneumothorax in the Treatment of Lobar Pneumonia BENJAMIN BURBANK and EMIL ROTHSTEIN 376
 Immunological Applications of Placental Extracts, Effectiveness by Oral Administration C F MCKHANN, A A GREEN, L E ECKLES, and J A V DAVIES 388

Fever Therapy in Gonorrheal Arthritis and Chorea	TRUMAN G SCHNABEL and FERDINAND FETTER	398
Dermatomyositis, Report of a Case with a Review of the Literature	I H MARCUS and JOSEPH WEINSTEIN	406
Fatal Diabetic Coma with Acute Renal Failure	MAYNARD E HOLMES	426
Incidence and Significance of the Roentgenologic Niche in Duodenal Ulcer	B R KIRKLIN and H A BURCH	436
Personality and the Endocrines, A Study Based Upon 1400 Quantitative Necropsies	WALTER FREEMAN	444
The Relationship of the Flat Chest to Intelligence	S A WEISMAN	451
Acute Lymphatic Leukemia in a Child of Four Years with a Severe Granulopenic Phase Preceding a Remission	LEWIS B FLINN	458
Case Reports		
An Instance of Possible Cirrhosis of the Liver Induced by a Hair Tonic Containing Carbon Tetrachloride	B B VINCENT LYON	470
Report of a Case of Left Ventricular Failure with Unusual Anatomical Changes in the Myocardium	H ROESLER and LOUIS A SOLOFF	477
Editorial		488
Reviews		490
College News Notes		493

NUMBER 5, NOVEMBER, 1935

The Mechanisms of Healing in Collapse Therapy	MAX PINNER	501
Lymphedema of the Extremities Etiology, Classification and Treatment, Report of 300 Cases	EDGAR V ALLEN and RALPH K GHORMLEY	516
The Experimental and Pathological Aspects of Silicosis	DUDLEY IRWIN	540
Accessory Sinus Infection, Its Relation to Mastoid and Lung Infections	WILLIS F MANGES	547
Basic Points in Roentgen-Ray Studies of Lung Anatomy and Pathology	KENNON DUNHAM and JOHN H SKAVLEM	555
Cardiac Output in Common Clinical Conditions, and the Diagnosis of Myocardial Insufficiency by Cardiac Output Methods	ISAAC STARR, JR and C J GAMBLE	569
Studies on the Increased Metabolism in Hyperthyroidism	E COWLES ANDRUS and DONALD MCEACHERN	579
Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis, Experimental, Clinical and General Considerations	I RHEUMATIC FEVER JAMES F RINEHART	586
Non-Traumatic Chylothorax and Chylopericardium, Review and Report of a Case Due to Carcinomatous Thromboangitis Obliterans of the Thoracic Duct and Upper Great Veins	WALLACE M YATER	600
Alterations in Hepatic Function Produced by Experimental Hepatic Lesions	JESSE L BOLLMAN and FRANK C MANN	617
Case Report		
Pancreatic Lithiasis	D B FAUST	625
Editorial		638
Reviews		641
College News Notes		643

NUMBER 6, DECEMBER, 1935

The Hemodynamics of the Circulation in Hypertension	J MURRAY KINSMAN and JOHN WALKER MOORE	649
---	--	-----

Vascular Disease in the Obese Diabetic, and in Non-Diabetics, A Discussion of Arteriosclerosis as a Cause of Diabetes	EDGAR C BECK, JAMES G FOWLER, EDWARD C KORNIG, and BYRON D BOWEN	662
Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis, Experimental, Clinical and General Considerations II Rheumatoid (Atrophic) Arthritis	JAMES F RINEHART	671
The Effects of Chronic Disease of the Liver on the Composition and Physicochemical Properties of Blood Changes in the Serum Proteins, Reduction in the Oxygen Saturation of the Arterial Blood	ALBERT M SNELL	690
Hypothyroidism A Common Symptom	ROGER I LEE	712
Clinical Relationships of Blood Cholesterol with a Summary of Our Present Knowledge of Cholesterol Metabolism	LEWIS M HURXTHAL and HAZEL M HUNT	717
Blood Cholesterol in Disturbances of the Basal Metabolic Rate	LEMUEL C MCGEE	728
The Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larynx and Trachea	ALVAN L BARACH	739
Symptomatic Psychoses in Pernicious Anemia	PAUL WM PREU and ARTHUR J GEIGER	766
Oleothorax Clinical and Experimental	J N HAYES	779
Case Reports		
Gonorrheal Septicemia and Erythema Nodosum	HENRY J BAKST, JOHN A FOLEY, and MARION E LAMB	790
Enteric Cysts	O B MAYER	797
Editorial		806
Reviews		808
College News Notes		812

NUMBER 7, JANUARY, 1936

Chemical Studies in Myasthenia Gravis	MILDRED ADAMS, MARSCHELLE H POWER, and WALTER M BOOTHBY	823
Metabolism of Creatine and Creatinine of Muscle Disease	A T MILHORAT and H G WOLFF	834
Experimental Thrombopenic Purpura, Cytological and Physical Changes in the Blood	LEANDRO M TOCANTINS	838
A Comparison of the Rate of Absorption from Normal and Burned Tissues	EDWARD C MASON, PEARL PAXTON, and H A SHOEMAKER	850
Studies in Multiple Sclerosis VIII Etiologic Factors in Multiple Sclerosis	TRACY J PUTNAM	854
Correlations of the Endocrine System	DAVID LANDBOROUGH THOMSON	864
Arteriosclerosis and Hypertension in Diabetes	HOWARD F ROOT and THOMAS P SHARKEY	873
The Present Status of the Problem of "Rheumatism" and Arthritis, Review of American and English Literature for 1934	PHILIP S HENCH, WALTER BAUER, A ALMON FLETCHER, DAVID GHRIST, FRANCIS HALL, and T PRESTON WHITE	883
Case Reports		
Ventricular Complexes of the Bundle-Branch-Block Type Associated with Short P-R Intervals	GEORGE H ROBERTS and DAVID I ABRAMSON	983
Excessive Smoking as a Possible Precipitating Factor in Diabetic Gangrene, with a Case Report	HARRY BLOTNER	987

Editorial	992
Reviews	996
Program of the 20th Annual Session—Detroit, March 2-6, 1936	999
College News Notes	1015
Notes on Medical Education and Medical Institutions in Michigan	1024

NUMBER 8, FEBRUARY, 1936

Growth and Development of Function in Blood Vessels and Lymphatics ELIOT R CLARK	1043
The Present Status of Bronchoscopy in Bronchial Asthma LOUIS H CLERF	1050
Prognosis in Acute Glomerular Nephritis ARTHUR B RICHTER	1057
The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice of Patients If the Amount of Alkali Is Not Varied PAUL H WOSIKA and EDWARD S EMERY, JR	1070
The Value of a Mixture of Powdered Milk and Alkali for Neutralizing the Gastric Acidity of Patients with Peptic Ulcer PAUL H WOSIKA and EDWARD S EMERY, JR	1078
Studies in Hypertension, A Proposed Classification of Hypertension Based upon the Nitrogen Distribution of the Serum Proteins HENRY A RASKY, ADOLPH BERNHARD, and GEORGE L ROHDENBURG	1091
Sedimentation Time in Acute Cardiac Infarction CHARLES SHOOKHOFF, ALBERT H DOUGLAS, and MRYER A RABINOWITZ	1101
Combined Medical and Surgical Management of Peptic Ulcer, with Em- phasis on the Treatment of Hemorrhage J W THOMPSON and H W SOPER	1106
Observations on the Effect of Sudden Changes in Arterial Tension in An- gina Pectoris E W BITZER	1120
The Practical Use of Hobbies in the Practice of Medicine JOHN R HAMILTON	1129
Case Reports	
Proliferative Intinitis of Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis, and Recurring Necrotic Ulcers of the Skin NELSON W BARKER and THOMAS W BAKER	1134
The Beneficial Effect of the Development of an Abnormal Rhythm with Slow Ventricular Rate in Circulatory Failure WILLIAM A COOKE	1143
A Report of Identical Albino Twins of Negro Parents ELMER G WAKERFIELD and SAMUEL C DELLINGER	1149
Editorial	1154
Reviews	1158
News Notes	1162

NUMBER 9, MARCH, 1936

Long-Standing Cases of Auricular Fibrillation with Organic Heart Dis- ease, Some Clinical Considerations WILLIAM A EVANS	1171
The Etiology of Abdominal Pain in Diabetic Acidosis HARRY WALKER	1178
Intensive Liver Therapy in Sprue PHILIP CORR	1182
Localization of the Site of Experimental Premature Contractions and Bundle Branch Lesions by Means of Multiplane Chest Leads Jo- SEPH WEINSTEIN and DAVID I ABRAMSON	1187

The Effectiveness of Acetyl-B-Methylcholine Given by Mouth as a Vaso-dilating Agent	GRACE A GOLDSMITH	1196
Blackwater Fever A Clinical Review of Fifty-Two Cases	M FERNÁN-NÚÑEZ	1203
The Treatment of Narcolepsy with Benzadrine Sulphate	HELMUTH ULRICH, CARL E TRAPP and BEN VIDGOLF	1213
Abdominal Distention in Lobar Pneumonia	JOEL GOLDMAN and ABRAHAM COHEN	1222
The Rôle of Accidental Puncture of Veins in the Production of Allergic Shock	G L WALDBOTT and M S ASCHER	1232
Schiller, the Greatest of the Medical Poets	LOUIS H RODDIS	1240
Case Reports		
Felty's Syndrome, Report of a Case with Necropsy Findings	ROBERT H WILLIAMS	1247
Neurocirculatory Asthenia Report of a Case Treated by Adrenal Denervation	JOHN P ANDERSON	1255
Paroxysmal Ventricular Tachycardia, Report of a Case Illustrating All the Diagnostic Criteria	AARON E PARSONNET	1258
Editorials		1266
Reviews		1268
Award of the John Phillips Memorial Medal to Dr E M Landis		1270
College News Notes		1271

NUMBER 10, APRIL, 1936

The Changing Order in Medicine	JAMES ALEXANDER MILLER	1287
Lymphopoiesis, Lymphatic Hyperplasia, and Lymphemia Fundamental Observations Concerning the Pathologic Physiology and Interrelationships of Lymphatic Leukemia, Leukosarcoma and Lymphosarcoma	B K WISEMAN	1303
Metabolism Studies in Myasthenia Gravis before and during the Administration of Glycine	MILDRED ADAMS, MARSHELLE H POWER, and WALTER M BOOTHBY	1330
The Treatment of Addison's Disease with Sodium Compounds, with the Report of One Case and the Summaries of Eleven Other Collected Cases Thus Treated	EDWARD C REIFENSTEIN and EDWARD C REIFENSTEIN, JR	1338
The Leukocyte Picture in Hodgkin's Disease	GRACE M ROTH and CHARLES H WATKINS	1365
The Interrelationship of Gastrointestinal and Renal Disease	HARRY GAUSS	1373
Further Observations on the Carotid Sinus Reflex	LOUIS H SIGLER	1380
Phosphatase Content of Human Serum in Pulmonary Tuberculosis Following the Administration of Vitamin D	PAUL D CRIMM and J W STRAYER	1393
Diagnosis of Dissecting Aneurysm of the Aorta	EDWIN E OSGOOD, M F GOURLEY, and RUSSELL L BAKER	1398
Diet of the Bluff Dwellers of the Ozark Mountains and Its Skeletal Effects	ELMER G WAKEFIELD and SAMUEL C DELLINGER	1412
Case Reports		
Terminal Hemorrhagic Nephritis A Case Exemplifying the Protean Character of Its Signs and Symptoms	IRVINE H PAGE	1419
Tonsillitis Associated with Acute Aseptic Meningitis	DAVID RIESMAN	1427

Intermittent Hydrarthrosis Associated with Undulant Fever	JOHN C SHARPE	1431
Editorial		1437
Reviews		1440
College News Notes		1442

NUMBER 11, MAY, 1936

The Rôle of Emotion in Disease	WALTER B CANNON	1453
Viruses and the Diseases Caused by Them	THOMAS M RIVERS	1466
Thrombopenic Purpura, An Analysis of 160 Cases	W M FOWLER	1475
The Therapeutic Effect of Solution of Potassium Arsenite in Chronic Myelogenous Leukemia	D J STLEPHENS and JOHN S LAWRENCE	1488
Adolescent Disturbances of Endocrine Function, the Importance of Their Recognition and Treatment	CHARLES H LAWRENCE	1503
Oxygen Treatment and Thyroid Ablation in the Treatment of Heart Disease	ALVAN L BARACH, DICKINSON W RICHARDS, and W BARCLAY PARSONS	1513
Therapeutic Action of the Nucleotides, the Treatment of the Whole Blood Picture with Ferrous Adenylate	SIMON L RUSKIN and ELIHU KATZ	1549
Hepatic Complications in the Treatment of Syphilis II Incidence of Hepatic Disease in Patients with Untreated Syphilis and during Their Subsequent Treatment	FREDERICK KELLOGG, NORMAN N EPSTEIN, and WM J KERR	1561
Neurological Symptoms in Posthemorrhagic Secondary Anemia	SAMUEL B HADDEN	1572
Case Reports		
Adenoma of the Parathyroid Gland, with Hyperparathyroidism	SAMUEL S RIVEN and MORTON F MASON	1578
Subacute Bacterial Endocarditis of the Mitral Valve Previously Rendered Incompetent by Infarction of the Papillary Muscle and Shortening of the Chordae Tendinae	I I LEMANN	1587
Diabetes Refractory to Insulin	SAMUEL S ALTSHULER and S E GOULD	1595
Editorial		1604
Reviews		1606
College News Notes		1609

NUMBER 12, JUNE, 1936

Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism	C N H LONG	1619
A Comparison of the Effectiveness of Glutamic Acid Hydrochloride and Dilute Hydrochloric Acid as the Replacement Therapy in Anacidity Measured by Fractional Gastric Acid Titration and Hydrogen-Ion Concentration Curves	HARRY SHAY and J GERSHON-COHEN	1628
The Medical and Economic Advantages of Roentgenographic Chest Survey of All Hospital Admissions	FRED JENNER HODGES	1639
Chronic Arthritis, a General Disease Requiring Individualized Treatment	ERNEST E IRONS	1658
Treatment of Pneumonia with Serum Containing Type-Specific, Heterophile, and Neutralizing Antibodies	VERNER B CALLOMON and JOHN UNGAR	1664

Some Factors in the Etiology of the Psychoneuroses	LOUIS CASAMAJOR	1677
Solitary Ulcer of the Ileum and Ulcer of Meckel's Diverticulum	PHILIP W BROWN and JOHN DEJ PEMBERTON	1684
Errors in the Interpretation of Cardiovascular Symptoms and Signs	PAUL D WHITE	1703
The Initial Ventricular Complex of the Electrocardiogram in Coronary Thrombosis	L FELDMAN	1714
Late Recrudescence in Encephalitis Lethargica with Succession of New Manifestations at Intervals of Years, the Problem of Prognosis	ALFRED GORDON	1725
Case Reports		
Renal Dwarfism, a Case Report	J F ROBERTS	1729
Acute Fulminating Meningococcus Infection, with Bilateral Capillary Hemorrhage of the Adrenals as the Most Striking Gross Pathologic Lesion, a Case Report	F H FOUCAR	1736
Lipoidal Histiocytoma (Fibroxanthoma), Report of a Case	GEORGE M LEWIS and WILBERT SACHS	1746
Editorials		1751
Reviews		1754
College News Notes		1757
Minutes of the Meeting of the Board of Regents		1763
Index		1785

ANNALS OF INTERNAL MEDICINE

VOLUME 9

JULY, 1935

NUMBER 1

PRESIDENTIAL ADDRESS *

By JONATHAN C MEAKINS, F A C P, *Montreal, Quebec, Canada*

It has been a custom of our College for the President to address you at least once a year and to take this occasion to deal with activities of the College, and incidentally such other subjects as it may please him to choose. Before proceeding with these matters I wish to take this opportunity of expressing my appreciation of the honor conferred upon me last year in electing me your President. Not only is it a great distinction to be chosen for this position by one's fellows in Internal Medicine, but also to be deemed worthy to follow in the footsteps of a lengthening line of America's most distinguished physicians. I sincerely thank you and hope that during my trusteeship the affairs of the College have not suffered.

The excellence of our Annual Clinical Meetings requires no eulogy from me. The taste we have had of the fare which Dr. Stengel and his committees have provided for us, speaks for itself. There is only one criticism, but hardly that, let me say complaint, that I might lodge. As each year passes our programs carry us to higher and higher heights in the medical stratosphere, and if we do not find some means of protection the concentration of the intellectual cosmic rays may consume us.

This Nineteenth Annual Clinical Session has, if possible, exceeded our anticipations of what such a meeting could be in Philadelphia. So I wish to express to Dr. Stengel and all of his colleagues our deep appreciation of the intellectual and social hospitality which they have provided for us. It has been indeed not only abundant and choice, but gracious. Our Annual Meetings are always most pleasant, particularly in renewing old friendships and making new ones. In particular, I take pleasure on this occasion in extending to the newly elected Fellows the friendly hand of welcome with the sincere wish that they will derive inspiration from their associations within the College. We must always remember that *we* are the College, and its success, reputation, and ideals are dependent upon the efforts and aspirations of one and all of us. The Board of Regents and the Board of Governors are but elected servants of the College. The success of our organiza-

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935

tion must depend upon the combined efforts of all as individuals and not upon the idealism of the few. The College has a great future but the steady progress toward its goal is the responsibility of each one of us. We must think as to where we are going and what is its eventual destiny. But more of this anon.

The joy of our yearly reunions is always tinged with a sadness for the absence of those who will be with us no more. Many we have called 'friend' and admired for their contributions to the progress of our profession and welfare of mankind. Others we had known but a short time but had hopes for greater intimacy and that personal association which binds the heart, the mind and the hand. I desire, on behalf of us all, Masters, Fellows, and Associates, to express our deep and sincere sympathy to the families and friends for their sad loss, and to assure them that wounds caused by the absence forever from our midst of our revered colleagues will only be healed by the Greatest of all Physicians.

It is now my duty to review in brief some of the activities which have occupied your Officers and Board of Regents since our meeting last year in Chicago. It is gratifying to record that the financial position of the College is one of solidity and is steadily improving. For this we are indebted in great part to the sagacity of our Treasurer and the Finance Committee, but also in an equally great part to our ever-watchful Executive Secretary, Mr. Loveland, and his Staff, who by economy and excellent executive ability have guided our ship through the contrary winds and tempestuous seas of these trying years. To him I wish to express our sincere thanks and appreciation for his fidelity to the interests of the College.

Our official journal, the ANNALS OF INTERNAL MEDICINE, has been under the capable guidance of the editor, Dr. Pincoffs, ably assisted by the Editorial Board. His task has not been an easy one. The duties of an editor I often think are the most exacting that can fall upon the shoulders of anyone. They require unremitting vigilance in so many directions, not the least of which is the selection of a comparatively few papers from so many offered, all of which must be carefully read and then assessed and balanced as to their acceptance. All are not equally suitable although excellent. He has a certain biblical rôle to play,—to paraphrase—"Many are offered but few can be chosen." I know it well, and it must be so, not that I have ever been an editor, but I have suffered by them, and on second thoughts I have seldom found them wrong. Writers, like artists, are apt to be touchy about the quality of their creations. Although these difficulties are a worry to the editor I am sure they are insignificant compared to the exasperations of delayed and changed galley proof and the lamentations and vituperations of the publishers. He, poor man, is between the upper stone,—the fond and temperamental parent of the manuscript, and the nether one,—a cold and profit-exacting printing press. But I am sure we all have confidence and first-hand knowledge that our Editor is serving the Annals excellently and for this we thank him.

Turning now to more general matters, one cannot dismiss the effect of the world-wide social turmoil of the past five years. Continents, nations and governments have been more or less blindly groping through a fog of shattered principles that appeared a short time ago to have been as firm as the rock of Gibraltar. It would be beyond the realm of possibility that our medical world would have escaped unscathed. Several of my predecessors have dwelt on certain aspects of this matter and it is not my purpose to deal with it at any length, but, certain phases have developed during the past year which must be, at least briefly, referred to. In the first place it must not be overlooked that our College is an international body. We are Fellows together for mutual help and guidance and the experience from experiments in one country or section may be of help to another, when not offered in any spirit of superiority but in a courteous and understanding manner as between friends. This is a vast continent and the problems of congested cities as compared with those of the farm, of the seaboard as compared to those of the great mid-land, have a greater divergence between the East and West than they have between the North and South of this continent. From whichever region we come, we must always cultivate a kindly and sympathetic appreciation of each other's difficulties.

Some six months ago your President, Mr. Roosevelt, in his wisdom, appointed a Medical Advisory Committee under the Committee on Economic Security, to study and advise on intricate and difficult problems which would naturally arise under any system of health insurance or other medico-social plan. I wish to inform you that the College happened to be well represented on this Committee by three members of the Board of Regents, not as College officials but entirely, I am sure, on account of their well merited reputation of being wise councillors in all matters which touch the honor and rights of the medical profession and our ageless trust, the welfare and health of all peoples. I merely touch on this matter here to assure you that the Board of Regents are not unmindful of the present trend of social affairs and are fully alive to the percussions they may have on the practice of Medicine. It would be presumptuous of me to make further comment, so here I leave the matter in the competent hands of my successor.

After these general remarks I wish to pass on and consider seriously certain matters which to my mind are of urgent concern at this moment. I am sure that many of us, from time to time, ask ourselves what the American College of Physicians really stands for and what its destiny should be. When we take stock, we can with pride point to our Annual Clinical Meetings and to our Journal which has a high standing among those devoted to the practical or clinical aspects of our profession. But, if we become a little more introspective and analytical, we must acknowledge that other associations and societies also have such meetings and publications for the broadcasting of their scientific and clinical erudition. Some of these are more exclusive than others. This exclusiveness, of course, is their own affair, undoubtedly determined by their policy, their ideals and their ob-

jectives As Dr Vincent so cleverly, but withal wittily, told us in Boston in 1929, there are different standards or criteria whereby the "elite" may be judged We, by our very name—"The American College of Physicians"—have abrogated to ourselves a certain aristocratic position or an "eliteness," if I may use the word, which we must justify in the eyes of the rest of the profession We call ourselves a College established primarily for the enrollment of "internists" or those of the medical fraternity or guild who devote themselves entirely to the profession of Medicine, as it is commonly known, to the exclusion of other methods of diagnosis and treatment Was such a movement necessary? And if so, why? And if these answers can be found satisfactory are we carrying it out in the proper manner or are we but another, rather exclusive and expensive, medical society?

To these questions I shall attempt to give answers and at the same time show, as I see it, a road upward to a bigger and better future for this College in and for which we have both faith and affection To do this I must ask you to bear with me for a short period while I review as briefly as I may certain historical events which I am sure you will find as pertinent to-day as they were in the distant past

If we search through the Acts and Ordinances of the fifteenth century in Great Britain we find in the reign of Henry VI, to be exact, 1460, a Royal Edict securing benefits and monopolistic rights to the Barber-Surgeon The exact reasons are not stated but presumably their prerogatives were being encroached upon by those whom they considered unfitted to practice the art,—in other words, the unqualified surgeons of the day This edict appeared to satisfy the London Barbers for nigh on one hundred years

In the meantime, the Surgeons in Edinburgh seem to have been in a bad way The country was in anarchy and chaos, the Barons were more powerful than the King (James IV), the people were oppressed and all forms of rascality ran riot The Surgeons, finding their profession invaded by all and sundry, petitioned the Town Council of Edinburgh to grant them an exclusive monopoly This was done in 1505 and was termed a "Seal of Cause" and confirmed in the following year by the Royal Authority Many decades pass without further mention of the activities of this craft They appeared to be the sole teachers and almost the sole practitioners in the city In 1589 they condescended to admit barbers to their corporation but these could not practise surgery or have any voice in the deliberations of their guild They had, indeed, exclusive privileges but these were being encroached upon by two descriptions of practitioners, the unqualified physicians and the unqualified apothecaries The former petitioned Cromwell to give them by means of a patent, power to elect themselves into a College, not merely for Edinburgh but for all Scotland They wished also to have power of examining and licensing apothecaries, of visiting the drug shops, and enforcing their authority It must be appreciated that the physicians of that day in Scotland were few and for the most part held foreign degrees The only Scottish University granting a medical

degree was St Andrews. The surgeons and apothecaries were alike in great alarm and scurried for safety by inducing the Town Council to constitute a Brotherhood (sic) of Apothecaries and Chirurgeon Apothecaries. The surgeons did not soon forget this attack on their monopoly and exerted every effort to maintain their exclusive rights, even fighting the University or Town College as well as the physicians.

We shall now return to London where the surgeons and barbers were apparently living in peace, but all was not well with the practice of the healing art. This I think is best appreciated from "An Act for the appointing of Physicians and Surgeons" in the third year of the reign of Henry VIII (1512). It reads in part as follows:

"To the King our Sovereign Lord, and to all the Lords Spiritual and Temporal, and Commons in this present Parliament assembled forasmuch as the science and cunning of Physick and Surgery (to the perfect knowledge whereof be requisite both great learning and ripe experience) is daily within this Realm exercised by a great multitude of ignorant persons, of whom the greater part have no manner of insight in the same, nor in any other kind of learning. Some also can no letters on the book, so far forth that common artificers, as Smiths, Weavers, and Women boldly and accustomedly take upon them great Cures, and things of great difficulty, in the which they partly use Sorcery and Witch-craft, partly apply such Medicines unto the disease, as be very noxious, and nothing meet therefore, to the high displeasure of God, great infamy to the Faculty, and the grievous hurt, damage, and destruction of many of the King's liege people, most especially of them that cannot discern the uncunning from the cunning, Be it therefore (to the surety and comfort of all manner people) by the authority of this present Parliament enacted, That no person within the city of London, nor within seven miles of the same, take upon him to exercise and occupy as Physician or Surgeon, except he be first examined, approved, and admitted by the Bishop of London, or by the Dean of Pauls, for the time being, calling to him or them four Doctors of Physick, and for Surgery, other expert persons in that Faculty, and for the first examination such as they shall think convenient, and afterward alway four of them that have been so approved."

And so on with due fines of five pounds for each month of illegal practice. It allows Bishops in other dioceses outside of London to approve also but only after proper examination, "Provided alway, that this Act nor anything therein contained, be not prejudicial to the Universities of Oxford or Cambridge." There is also a memorandum "That Surgeons be comprised in this Act as Physicians."

It will be noted that this but enacts how the privilege of practising Medicine should be obtained and who should grant it.

At this time the great Thomas Linacre was physician to Henry VIII.

and the foremost physician of his time. The life of Linacre is not part of our present thesis. One of his great labors alone interests us, namely, the creation of the Royal College of Physicians of London. He undoubtedly got the idea during his period in Padua where he obtained his Doctorate of Physick with applause. The organization and ideals were his own as was also the great part of the expenses, the gift of the Crown was limited to the grant of the letters patent. "The wisdom of Linacre's plan speaks for itself. His scheme without doubt was not only to create a good understanding and unanimity among his profession, which of itself was an excellent thought, but to make them more useful to the public, and he imagined that by separating them from the vulgar empirics and setting them upon such a reputable foot of distinction, there would always arise a spirit of emulation among men liberally educated, which would animate them in pursuing their inquiries into the nature of diseases, and the methods of cure, for the benefit of mankind, and perhaps no founder ever had the good fortune to have his designs succeed more to his wish."

Linacre's efforts were undoubtedly crowned by the creation of the first real College of Physicians or Surgeons in either England, Scotland or Ireland. Companies or Guilds of Surgeons or Barber Surgeons certainly preceded this College but they were not founded on the same ideals for the advancement of learning. These ideals were emulated by others but all must pay tribute for the inspiration to such lofty thoughts. I shall not weary you with further detail of this pioneer College. It grew from strength to strength. The names of its Fellows form a constellation of such brilliancy as to be the envy and admiration of all—John Caius, Francis Glisson, William Harvey, Richard Lower, John Radcliffe, Robert Sibbald, Hans Sloane, Thomas Sydenham, Thomas Willis, Edward Wotton, and a host of others.

Whereas the Surgeons and Barber Surgeons undertook the teaching of their art after the manner of having apprentices, the Royal College of Physicians early began to give organized lectures and demonstrations, and consequently became the first center of medical education in the British Isles outside of the Universities. It will be remembered that William Harvey demonstrated and taught the circulation of the blood in his Lumleian lectures in 1616, twelve years before his first publication. All of those who obtained the privilege of the practice of Physic were not Fellows, the more junior branch were Members and could become Fellows only after a demonstration of their exceptional worth.

The physicians of Ireland and Scotland were not so fortunate as their London colleagues in obtaining early recognition. It was not until 1668 in Ireland, and 1681 in Scotland, that they obtained their Royal Charters. They were substantially framed upon the Royal College of London. They all threw their energies into teaching and granted after examination license to practise not only to those vouched for by themselves but graduates of Universities from the Continent and elsewhere. In fact, they were the

more progressive factors in medical education being rivalled by few of the Universities. This naturally stimulated the Companies and Guilds of Surgeons to put a better foot forward. For example, in Edinburgh the teaching of surgery had been at a rather slothful level until 1681 when the Royal Charter was given to the Physicians. They then bestirred themselves and put their house in order, and sought and obtained in 1694 what is stated to be the first authority in Scotland to carry out dissection and from such cadavers teach anatomy. The English surgical fraternities had moved much earlier but it is doubtful whether they taught anatomy except as a purely practical demonstration. They did not reveal any semblance of reaching the anatomical and physiological experimental accomplishments of the physicians during the seventeenth and eighteenth centuries. But still they slowly and surely progressed in organization until in 1784 the Royal College of Surgeons of Ireland, and in 1800 the Royal College of Surgeons of England, obtained their Charters as Colleges as distinct from Companies or Guilds. During the eighteenth century there is no doubt that all these Colleges and Guilds ably seconded the Royal College of Physicians of London in medical education. There were undoubtedly times when certain branches of teaching excelled in different centers,—for instance, the great Edinburgh School of Anatomy from approximately 1720 to 1830, or the London Surgeons of the latter part of the eighteenth century, and the Irish School of Physicians of the middle of the nineteenth century. But taking it all in all the physicians of the Colleges of London and Edinburgh left a lasting trail of high accomplishment until Simpson and Lister laid the foundations of modern technical surgery.

The point I want to make is that during four centuries these Royal Colleges of Physicians and Surgeons took a place not second to the Universities in medical education. They ranked equal to them in the certification or licensure of the medical practitioners and it was not until 1858 that the General Medical Council of Great Britain was created and invested with the sole power of assessing the "regular" and the "unregular" practitioner of medicine.

But did these Colleges do nothing else? Assuredly they did! They had an additional function which in our time has made them great and their Fellows honored and respected with cause. The certification of practitioners of Medicine and Surgery was not their sole function. They held out a higher ideal of accomplishment in the fact that to become a Fellow was a high distinction which was attained only after passing rigid examinations which gave evidence of superior accomplishments. As time passed, this naturally gave to them great power and also responsibility. In short, the bestowal of the hall-mark of the compleat physician or surgeon was the sole privilege of these Colleges and this they did by virtue of elevation to Fellowship of those they deemed worthy. So great was the faith in their award that it became the custom to require a certification of Fellowship in a Royal College of Physicians or Surgeons of all applicants to positions in hospitals.

or teaching institutions of rank. This has been criticized as working hardship and favoritism on behalf of a relatively privileged few. The unfavorable but rare exceptions undoubtedly have occurred but these have accentuated the wisdom of the generally accepted rule. The Colleges have always been conscious of their responsibility and have erred, if anything, on the side of strictness for admission to Fellowship because of this trust.

The custom of having only Fellows of the Royal Colleges on the senior staff of the larger hospitals and on the faculty of teaching institutions dates back several centuries. The juniors may be Members of the Colleges of Physicians but Fellows only are eligible to the senior posts. This custom has operated to the benefit of the Colleges as well as the institutions. In the first place it required that the Colleges maintain a high level for their requirements. They have jealously guarded their reputation not only for professional ability but also for ethical standards. Institutions and the laity, on the other hand, have trusted their hall-mark to be worth always its face value and have seldom been disappointed. The Fellowship was a guarantee that the possessor had satisfied his peers that his training and knowledge of the specialty he professed were of such quality, and had been so tested by an impartial examination as to warrant them to bestow upon him this accolade of the elite. During the past 75 years this responsibility has become greater through the rapid progress of both medicine and surgery and the increasing need of broad and special knowledge.

But they have also through these centuries contributed other great boons to the medical profession. The physicians have developed their libraries and the surgeons their museums to the everlasting benefit of the profession. There has been, indeed, something of beautiful simplicity in their tacit acceptance of these responsibilities without carping rivalry but with sweet cooperation and help in each other's task.

What influence have these Colleges exerted on the rest of the English-speaking world? This question may be briefly dealt with under three headings. (1) For several centuries large numbers of young men from the Dominions and the United States flocked to them for both undergraduate and postgraduate training—the latter to aspire to a Fellowship and return, perchance, to their native lands with the accolade of their Order. (2) Their example influenced others to emulate them after a fashion. In North America there are the Colleges of Physicians and Surgeons of New York, Baltimore, of Ontario, of Quebec, and many others. But they have confined their activities almost entirely to undergraduate teaching or to the task of being more or less active Examining Boards for local licensure. There is, however, one College of Physicians in North America *par excellence* which I think I might specifically mention this evening with propriety—that of Philadelphia. There seems but little doubt that years ago some of the young men of this city after graduating from the Medical School of the College of Philadelphia went to Edinburgh and London to complete their studies, and were fired with the ambition

to found a College here Dr de Schweinitz reminds us that Samuel Powel Griffiths in 1783 expressly states that the idea of an American College of Physicians had several times occurred to him and three years later (1786) the College of Physicians of Philadelphia was founded I have often wondered why the city claimed preference over the new Nation—probably the example of London and Edinburgh was the potent influence particularly as the Royal College of Physicians of London served as the prototype Also, it must be remembered that it was not until 1800 that the Royal College of Surgeons of London received its Charter and in 1843 acquired the greater appellation of “England” The Constitution of the College of Physicians of Philadelphia has a nice familiar tone when compared with the Charter undoubtedly drawn up by Linacre over 250 years before—even to the four censors Their careers have also been somewhat alike in their duties to their community and the perfection of their library The difference, however, is clear cut and fundamental Teaching in the broad sense and admission by examination have not been among the functions of the Philadelphian College Undoubtedly conditions were different but for all that it created a medical aristocracy which for the greater influence was too exclusive

(3) We now come to a third phase which has been born of a condition of affairs strangely similar in principles although not in detail with the conditions in the sixteenth and seventeenth centuries Then the Corporation, Guilds and Colleges were formed to protect the public from “the multitude of ignorant persons”—“common artificers, as Smiths, Weavers and Women” who “boldly and accustomably take upon them great cures”, in other words, those who assumed knowledge which they did not have and imitated the honest practitioner of the day By our State and Provincial Boards and other agencies we have imitated this function of the British Colleges, but only insofar as the general practitioner is concerned and not for those who profess to be specialists in Medicine and Surgery

Here we arrive at the point where events indicate that such a College as ours appeared to be necessary This necessity did not seem to have been a local need or confined to physicians or internists alone Since 1913 five new Colleges in the English-speaking world, with aspirations more or less similar to the older order, have come into being,—The American College of Surgeons, The American College of Physicians, The Royal College of Physicians and Surgeons of Canada, The British College of Obstetricians and Gynaecologists, and The Royal Australasian College of Surgeons—five new, more or less exclusively elite, bodies in 22 years—one every 4 years The whole range of the broader specialties of medical practice is represented So now we come to our second question Why was this spontaneous and widespread movement apparently necessary? Is medical practice in a somewhat similar position today to what it was four centuries ago in that those who are unqualified are presuming to invade the seats of the mighty? There seems little doubt that this is the answer During

the past generation specialism in many branches of medicine has become rampant and has been professed by many who had no adequate preparation or right to do so and furthermore human nature has changed but little since the days of Henry VIII when it was deemed necessary to protect "most especially them that cannot discern the uncunning from the cunning" So, here we have the answer to our second question, namely, to hall-mark those who have equipped themselves by special study and application to practise one or other of the senior branches of the medical art and science as distinct from those who have not so prepared themselves but would have the public believe that they have and so profess to all and sundry To control such unwarranted assumptions has become the principal function of our elder sisters

Are these younger Colleges trying to emulate the exclusiveness of their seniors in this matter? If so, it would be well to be thorough in the matter Such a College or Society or Association must have certain standards for admission But then all those that are reputable have This now brings us to the difference between an association or a society and a college—not entirely the same significance it had in Roman law but what it has come to signify at the present day I make bold to hold that it implies that it is only possible for one to enter the body of its membership after he has duly satisfied the appointed examiners or censors—call them what you please—by adequate and impartial tests of his worthiness In a small or local community such tests are easy of application and so it was found by our older sisters, but as their fame spread and applicants presented themselves who were not known in person, or came from foreign countries or from lands across the seven seas, many of them near neighbors compared to our States and Provinces, the difficulties to enforce equality of standard became insurmountable without a uniform and impartial examination

Gentlemen, we are at the parting of the ways What other Colleges may do is their affair and none of our business, but what our future will be most certainly is our deep concern Our Credential Committees have labored for years with an almost Herculean task—they have given of their best—but it is beyond human capacity to be arbiters of our membership from the information required and be satisfied that you have been fair and just to the College and the petitioners for membership Are we to remain a rather select association and, as I have already said, an expensive one, or are we to be a College of Physicians to which its Fellows have been elected after passing such tests and examinations—moral, spiritual, and scientific—as to warrant the confidence of our people to trust him above those who are not, wheresoever he may go? That is the acid test! We as a College are responsible that it should be so and if we cannot command this we have failed in our self-appointed task, and our hall-mark of F A C P is of little worth I do not wish to convey the impression that we have altogether failed, but I am thoroughly convinced that our methods

of assay must be improved until the world knows and has confidence in the products of our mint

Now I am through! I thank you for your patience in enduring my rather domestic sermon but I have cogitated this matter for many years and believe that I am right and that history of the past supports me and that of the future will justify my belief

In conclusion I want again to thank the College for bestowing upon me the highest honor that can come to an American Physician To my colleagues, the Officers, the Board of Regents, and the Board of Governors I wish to say an official and public farewell and thank them all for their unfailing support and courtesy during my tenure of office I bid you all good luck and godspeed!

PRESENTATION OF THE JOHN PHILLIPS MEMORIAL MEDAL TO PROFESSOR LEO LOEB, OF WASHINGTON UNIVERSITY

Ladies and Gentlemen

It is a custom of our College to award each year a medal in memory of our revered colleague, John Phillips. This medal is in token of notable contributions to the Science of Medicine. In awarding it this year your Board of Regents had in mind the rich accomplishments of a life-time devoted to researches in the Medical Sciences. During approximately forty years of active work Professor Loeb has contributed to many fields of general and experimental pathology. His first researches concerned the transplantation of pigmented skin which developed into a study of the main factors underlying transplantations in general and led to an analysis of organismal differentials and individuality in various life processes.

Early studies of wound healing led to investigations into the mechanism of growth, tissue culture and tissue formation in general and served as a model in the analysis of factors active in wound healing and inflammation.

His well known pioneer work on the transplantation of malignant tumors in animals made possible the study of heredity in tumors and the first quantitative determinations of this factor. Investigations concerning the relationship between hereditary factors and internal secretions in the origin of tumors led to a study of those of the ovary, the mechanism of the underlying sex cycle and to an analysis of certain hormones of the anterior pituitary and their significance for the ovary and the thyroid gland.

Since 1929 Professor Loeb has actively pursued his investigations of the action of the thyroid-stimulating hormone of the anterior hypophysis. In a long series of contributions on this subject, he has demonstrated in experimental animals increased mitotic activity of the thyroid cells, changes in the iodine content of the thyroid gland, elevation of oxygen consumption, accelerated circulation, exophthalmos and indeed most of the symptoms of Graves' disease.

Professor Loeb,—in recognition of these and many other notable contributions to Science, it gives me great pleasure and honor, on behalf of the American College of Physicians, to hand you this John Phillips Memorial Medal.

PHILLIPS MEMORIAL PRIZE ORATION

THE THYROID STIMULATING HORMONE OF THE ANTERIOR PITUITARY GLAND

By LEO LOEB, *St Louis, Missouri*

MAY I express to you, Mr President and to the American College of Physicians, my deep appreciation of the honor you have conferred upon me. It is an interesting coincidence that you have invited me to discuss before you the thyroid stimulating hormone of the anterior pituitary gland here in Philadelphia, where about 30 years ago I began my investigations of the problems concerning internal secretions. At that time, I studied the functions of the corpus luteum and I found that one of its hormones sensitized the uterine mucosa so that when, subsequently, mechanical stimuli reached it, the maternal placentae or experimental placentomata were produced. In addition it could be shown that the corpus luteum prevents ovulation. These investigations in the course of time led to the study of the mechanism underlying the sexual cycle, which I have followed ever since. But about 16 years ago, I became also interested in the interrelations between various glands of internal secretion and I began to investigate the interactions between the thyroid gland and other glands with internal secretions, in particular the anterior pituitary. At first, I used in this work a commercial preparation of anterior pituitary gland, which evidently contained an admixture of thyroid substance and the latter predominated over the anterior pituitary substance proper. In the meantime biologists had made the interesting discovery that thyroid substance with its hormone is a necessary stimulant for metamorphosis in amphibia and that also anterior pituitary substance can exert a similar effect on metamorphosis provided the thyroid gland is present at the same time. The pituitary substance evidently acted by way of the thyroid gland, it stimulated the latter to function, as the studies of Allen, P. E. Smith, Uhlenhuth, Spraul, Hogben and Hoskins have shown, and Uhlenhuth in particular noticed, during this process, indications of an enlargement of the thyroid acini and of an increased secretion of the acinus cells. This effect of the thyroid on amphibian metamorphosis was subsequently introduced, as a test for the presence of thyroid hormone, into experimental pathology and clinical medicine and proved of value—an example of fruitful cooperation between pure biology and clinical medicine. It was also shown by P. E. Smith and Foster that extirpation of the anterior pituitary in rats led to an atrophy of the thyroid gland.

About seven years ago, we began a reinvestigation of the relation be-

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935
Department of Pathology, Washington University School of Medicine, St. Louis, Mo

tween anterior pituitary and thyroid gland, but this time we used our own anterior pituitary preparation and, as in our previous investigations, it was the guinea pig which served as test animal. Very soon it was found that after a few injections of this anterior pituitary extract, which was obtained from cattle, the whole appearance of the thyroid gland changed radically. The colloid softened and was absorbed, the acinus cells became high cuboidal and cylindrical. The acini changed their shape. Instead of round acini, lined with rather low cuboidal cells, there developed longitudinal, often curved, winding slits lined with high cylindrical cells. It was difficult to identify in the microscopic picture the gland thus produced with the thyroid, and yet it closely resembled the thyroid gland as found in very pronounced cases of Graves' disease or exophthalmic goiter, where nature has apparently made a similar experiment. Moreover, we observed that, during the period of injections of anterior pituitary extracts, the animals lost weight. This suggested the possibility that through longer continued injections the other principal symptoms of Graves' disease might also be imitated. With the cooperation of our associates—and soon others also began to take part in this work—this possibility was realized. It is an interesting experience to follow how step by step the symptom-complex of Graves' disease was reproduced in the guinea pig. In addition to the structural changes in the thyroid gland itself similar to those characteristic of severe cases of this disease and to the loss in body weight, the basal metabolism rose considerably, the eyes of the animal began to protrude, tachycardia and nervousness, as indicated by an intensified reflex activity, became manifest. The glycogen in liver and muscle was mobilized and the adrenal cortex showed considerable increase in cell divisions. The stimulation of the thyroid gland led to solution processes in the colloid and thus to a constant discharge of an increased amount of organic iodine into the blood stream. Therefore the blood became richer in these organic iodine compounds, among which thyroxin is especially important.

In this connection it may be of interest to refer briefly also to the action of inorganic iodine on the thyroid gland. Under ordinary conditions this kind of iodine stimulates the thyroid gland. But if inorganic iodine is given concomitantly with anterior pituitary hormone, it inhibits the latter in its stimulating action on the thyroid gland and thus it resembles thyroid hormone which invariably inhibits the functioning of this organ. Now, it is well known, especially through the observations of Plummer, that also in exophthalmic goiter iodine at least temporarily reduces the activity of the thyroid gland and makes an operative removal of this organ possible in otherwise unfavorable cases. We notice then an almost complete correspondence between the effects of the injections of extracts of anterior pituitary of cattle into guinea pigs and the symptom complex of Graves' disease.

There still remains to be considered the correlation between the stimulation of the thyroid gland and the changes which take place in the ovary

under the influence of the hormones of the anterior pituitary. If we inject acid extract of cattle anterior pituitary into female guinea pigs, we notice a destructive effect exerted by this substance on the ovarian follicles, which undergo an early retrogression (atresia). At the same time, the theca interna may manifest a slight degree of luteinization in certain atretic follicles and occasionally a large follicle may become converted into a pseudo-corpora luteum. Similar is the effect of the extract of anterior pituitary of hog and sheep. The implantation of the glands from these species acts in a corresponding manner to the injection of extract, although the effects of the injections are slightly more pronounced. If we implant one or two guinea pig anterior pituitaries, noticeable hypertrophy of the thyroid is usually lacking, there is induced merely the formation of very large ovarian follicles, the granulosa of which matures, and of some strands of interstitial gland in the medulla of the ovary. But if we implant several guinea pig anterior pituitaries into a female guinea pig, the effects may become more intense in the ovary and at the same time a slight hypertrophy may appear also in the thyroid gland. Anterior pituitaries of rat, of rabbit and of man cause marked luteinization of the granulosa, as well as of the theca interna, and these processes are accompanied by a noticeable hypertrophy of the thyroid gland, but the different species may again show certain minor variations among themselves. We see then that the experimentally produced hypertrophic changes in the thyroid gland, as a rule, are associated with definite changes in the ovary of the guinea pig, it does not therefore seem advisable to us at present to apply to the thyroid stimulating hormone the term thyrotropic, in the sense that the action of this hormone is limited to the thyroid gland. We further notice that the effects of the anterior pituitary glands from different species are in certain respects specific.

In regard to the various changes induced by introduction of anterior pituitary gland some of these are the result of the stimulation of the thyroid gland and may therefore be considered as indirect changes. This applies especially to the effects on metabolism, heart rate, reflex action and presumably on carbohydrate metabolism, but it does not apply to the effects on the ovary, the destructive action which cattle anterior pituitary exerts on the ovarian follicles is not caused directly by thyroid hormone, as experiments in thyroidectomized guinea pigs indicate. On the contrary the thyroid hormone itself seems to cause an increased growth of the ovarian follicles. It is also probable that the effects on the eye and on the adrenal gland do not take place by way of the thyroid gland.

If we may then be able to state that, by inducing experimentally an increased activity of the anterior pituitary gland in the guinea pig, it is possible to reproduce the essential symptoms of Graves' disease in man, this does not necessarily mean that increased activity of this gland is the essential factor underlying Graves' disease, but it suggests, at least very strongly, that in some way the anterior pituitary is involved in this condition. However, there is apparently one serious objection to such a con-

clusion, namely the fact, observed by us several years ago and since confirmed by Collip and Anderson and others, that if we continue the injections of anterior pituitary extract for a long period of time, the thyroid gland as well as the sex organs step by step return to their normal state. On the other hand, we know that Graves' disease is not as a rule a self-limiting disease, although remissions may take place. When we first made this observation concerning the establishment of an active resistance to injections of anterior pituitary extracts, we pointed out the possible significance of this occurrence as an explanation of remissions in Graves' disease. It is possible that, after a cessation of the administration of the extract continued over a longer time, injections might again become effective, and the resistance thus established might in reality correspond to a remission.

As to the mechanism underlying this acquired resistance, we found in our first experiments that the blood serum of the resistant animals does not exert a direct neutralizing action on the hormone. More recently Collip and Anderson have made the important discovery that through injection of such serum it is possible to induce in the injected animal reactions, of an as yet unknown nature, which somehow counteract the effects of the hormone, at least for a certain period.

It is, however, conceivable that other mechanisms, which have been shown to function in the development of resistance and which exert their influence primarily by acting on tissues and organs in a specific manner, may secondarily cause the entrance into the circulation of substances which inhibit the response of tissues to the stimulating action of anterior pituitary hormone. We were able to demonstrate that as stated iodides, as well as thyroid hormone, inhibit the effect of the anterior pituitary hormone on the thyroid gland, largely in all probability by diminishing the responsiveness of the thyroid gland to this hormone. Thus a self-limiting mechanism can be shown to exist. Anterior pituitary hormone stimulates the thyroid gland, following this stimulation, thyroid hormone is given off in increased amounts into the circulation and the latter substance then counteracts the effect of the anterior pituitary hormone. But there is a second self-regulatory mechanism, which likewise tends to limit thyroid activity. As a result of the secretion of thyroid hormone, the basal metabolism is increased and this increase usually leads to a loss in weight of the individual thus affected. Now, in experiments with guinea pigs, a loss in body weight in itself tends to cause a return of the thyroid gland to a resting state. The acinar epithelium becomes low, the acini small and the colloid hard. Under such conditions the amount of thyroid hormone given off into the circulation would be reduced and the effect of the thyroid stimulating hormone would be limited. There are in addition indications that still other mechanisms of a cellular nature may exist which tend to regulate and restrict thyroid activity, this follows from the rapidity with which the multiplication of acinar cells in the stimulated thyroid gland begins to decline, notwithstanding the continued application of the stimulus.

It has recently been suggested by Kuschinsky, as well as by Loeser and Thompson, that the stimulating action, which iodine exerts on the thyroid gland, as well as the inhibiting action of thyroid hormone, is mediated by the anterior pituitary gland. While it seems probable that the anterior pituitary gland is indeed concerned in such effects, still there are reasons for the conclusion that these substances act also directly on the thyroid gland.

There is another consideration which has some bearing on the question with which we are here primarily concerned, namely the significance of the anterior pituitary gland in the etiology of exophthalmic goiter. Clinical observation points to the importance of an inner constitutional factor, supplementary to the stimulating factor, in the origin of this disease, as is the case in so many other diseases. This constitutional factor may modify the response of the organism to the stimulating factor, and thus prevent the full effect of mechanisms which otherwise might tend to counteract the hormone action in normal individuals.

Considering the preponderating influence, which the anterior pituitary gland, by way of its hormone, exerts on the thyroid gland, on the growth of the latter and on its metabolic activity—two functions which as a rule seem to go hand in hand—as well as the fact that all the principal symptoms of Graves' disease can be reproduced by administration of the thyroid stimulating hormone of the anterior pituitary gland, there seems to be some justification for the belief that the action of the anterior pituitary is involved in the etiology of Graves' disease, although it may be only one of several factors concerned in this condition. However, though the experimental reproduction of a disease complex may make it very probable that the disease itself originates in a similar manner, still it does not afford conclusive proof. While it may be difficult to furnish such a conclusive proof, several lines of investigation suggest themselves, and we have recently undertaken experiments which, we hope, may lead to a more direct answer to this problem. One of the difficulties which we have to face at present is the lack of definite knowledge as to the number and kind of hormones which are produced in the anterior pituitary gland. So far, we merely know the effects initiated by substances given off by this organ and acting as hormones. However, quite recently with the cooperation of our associates, we have found a method which permits us experimentally to suppress at will certain activities of the anterior pituitary gland, while enhancing others, and to transform the action of the anterior pituitary gland, which is characteristic of one species, into that of a different species.

These recent investigations which are not yet finished, seem to confirm tentative conclusions which we had drawn on the basis of previous observations, namely that as far as the action of the anterior pituitary gland on the ovary is concerned we may distinguish in the main two substances, namely a follicle-stimulating hormone, which also induces maturation processes in the follicles, and a second substance inducing atresia which means destruction of follicles. The latter action may be associated with a very

moderate formation of pseudolutein and interstitial gland tissue. This effect may perhaps be due to a third substance. It can be shown experimentally that the anterior pituitary glands of different species differ as to the relative preponderance of these substances. The possibility of separating thus these substances acting on the ovary and the associated thyroid stimulating hormone by experimental chemical means, may, we hope, open the way for approaching in a more direct manner the problem as to the significance of the anterior pituitary gland in the etiology of Graves' disease.

Let me say in conclusion that I am fully aware of the incompleteness of these investigations at the present time, and also of the fact that whatever has been accomplished is due to the cooperation of my associates and of other investigators. But may I also be permitted to point out that these investigations very well exemplify the advantages which accrue to clinical medicine from cooperation with biology, physiology and experimental pathology. They all should be encouraged to proceed in their own way and to seek their own problems. At some point they will meet for fruitful association. They are not sharply separable and essentially they form one connected whole. While the cure of disease is the direct aim of clinical medicine, the analysis of man and life, in relation to the environmental factors operating in the universe, at which biology aims, will help the physician to approach, with a broader understanding and deeper sympathy, the problems which his patient faces, in a world to which after all our body and mind are not fully adapted.

THE PRESENT STATUS OF ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF LOBAR PNEUMONIA

By SIMON S. LEOPOLD, M.D., F.A.C.P., and LOUIS M. LIEBERMAN, M.D.,
Philadelphia, Pennsylvania

THERAPEUTIC innovations begin with an original idea or more often with a new application of an old one and if promising and spectacular, may be followed by premature and unjustified optimism. After experimentation and thorough clinical trial have established their status, they are either accepted or rejected.

In connection with the therapeutic use of pneumothorax in pneumonia we have passed through a period of enthusiasm which was initiated primarily by empirical use of the method, and only later obtained the confirmation of experimental evidence. That this order was the reverse of what it should have been is beside the point.

The past year has been devoted to further animal experimentation and more thorough clinical trial and, although insufficient time has elapsed to warrant final judgment, enough information is available to permit the expression of certain opinions derived from a critical analysis of the data. We are concerned with the reports on 197 cases of lobar pneumonia which have either appeared in print or have been submitted to the authors prior to publication. This latter courtesy is herewith gratefully acknowledged.

The following table lists the names of authors, the number of cases in each report, and the mortality rates.

It is an accepted fact that the mortality of lobar pneumonia in general

TABLE I

Number of Cases and Mortality of Lobar Pneumonia Treated by Artificial Pneumothorax
(American authors March 1934 to April 1935)

Authors	No of Cases	Died	% Mortality
Blake, Howard and Hull ^{1,2}	43	11	25.5
Robertson, Behrend, Cowper and Tuck ^{3,4,5}	51	20	39.2
Stoll ⁶	29	7	24.1
Leopold and Lieberman ⁷	16	5	32.0
Moorman ^{8,9}	10	3	30.0
Isaacs, Udesky, de Pinto ¹⁰	7	4	57.1
Hammond ¹¹	7	1	14.3
Crowell ¹²	4	1	25.0
Hines and Bennett ¹³	12	4	33.3
Holmes and Randolph ¹⁴	18	2	11.1
Totals	197	58	29.4

*Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

From the Medical Division and the Thoracic Clinic of the Hospital of the University of Pennsylvania.

hospitals throughout this county ranges between 25 and 35 per cent. Therefore, it would appear that therapeutic pneumothorax has been neither helpful nor harmful and has had no influence on the death rate of this disease. This statement is true and will continue to be true if this treatment is used as indiscriminately in the future as it has been in the past.

The mortality from lobar pneumonia under any form of treatment, specific or non-specific, is conspicuously influenced by age, type of pneumococcic infection, bacteremia, spread, and postpneumonic complications. The results of specific serum therapy depend largely on the day of the disease on which such treatment is instituted. Early treatment is even more important when artificial pneumothorax is used.

In addition to the above named factors, there is one more which may be disregarded under the usual methods of treatment but which is of fundamental importance in compression therapy. Preexisting fibrous pleural adhesions render this type of treatment inadequate or useless. Recent pleural adhesions, developing as the result of the extension of the acute infectious process from the lung to the adjacent pleura, may have a similar effect.

Let us proceed to analyze the cases treated by artificial pneumothorax in relation to those factors which most significantly influence mortality. This task is made difficult in many cases by the multiplicity of determining factors, such as the coexistence of bacteremia and spread.

Age After infancy, and during childhood, lobar pneumonia is a comparatively innocuous disease with a mortality of 3 or 4 per cent. The incidence of empyema in infancy and childhood is 12 per cent. It is apparent from a survey of the cases in infancy and childhood treated by artificial pneumothorax that there is greater likelihood in them of spontaneous pneumothorax and empyema. We do not believe that this method of treatment should be employed in this group and we can see no possible justification for its use in the treatment of late post-pneumonic complications as practiced by several continental writers^{15, 16, 17, 18}

At the other extreme of life the greater probability of chronic adhesions and the increased prevalence of Type III infection which may produce a plastic exudate interferes with but does not contraindicate compression therapy.

Day of Disease It is apparent that too few authors have been sufficiently impressed by the fundamental importance of early treatment and many cases have been treated too late. Most of these should not have had therapeutic pneumothorax. Blake's complete statistics which have been placed most generously at the writer's disposal prior to their publication are most instructive. He treated one case on the first day, seven on the second and 17 on the third. Of these 25 cases, one died—with bacteremia and contralateral spread. Twenty-four recovered. Sixteen were treated on the fourth day and two on the fifth. Of these 18 cases 10 died.

This is tremendously significant in view of the fact that the average age of the recovered cases was 33.5 years while the average age of the fatal

cases was 43 years—a difference which cannot possibly explain a mortality of 4 per cent in those treated within the first three days compared to a mortality of 55.5 per cent in those treated on the fourth and fifth days.

Bacteremia The incidence of bacteremia and its attendant mortality in 128 treated adult cases is shown in table 2.

TABLE II

Incidence of Bacteremia and Mortality in 128 Adult Cases of Lobar Pneumonia Treated by Artificial Pneumothorax

Authors	No of Cases	Died	Bacteremia	Died
Blake, Howard and Hull	43	11	12	7
Stoll	29	7	5	5
Leopold and Lieberman	16	5	5	1
Behrend, Tuck and Robertson	40	14	5	4
Totals	128	37	27	17

The incidence of bacteremia was 21 per cent and its mortality was 63 per cent. From this small series of cases, no deductions can be drawn regarding the effect of artificial pneumothorax on bacteremia except to say that it is of no apparent value when first employed after blood stream invasion has occurred. Much more experimental work must be undertaken and many more patients will have to be treated early and effectively before any conclusions can be drawn in regard to the value of compression therapy in preventing blood stream invasion.

Spread The incidence of spread, determined clinically, in lobar pneumonia is about 10 per cent, at necropsy 16 per cent. The mortality is almost doubled when two or three lobes on the same side are involved and is nearly tripled when both lungs are implicated. The following table shows the incidence and mortality of spread in 86 treated cases.

TABLE III

Incidence of Spread and Mortality in 86 Adult Cases of Lobar Pneumonia Treated by Artificial Pneumothorax

Author	No of Cases (Early)	Spread	Died	No of Cases (Late)	Spread	Died
Leopold and Lieberman	11	3	3	5	2	1
Blake, Howard and Hull	25	3	1	18	8	6
Isaacs, Udesky and de Pinto	4	1	1	3	2	2
Hines and Bennett	2	1	1	10	1	1
Holmes and Randolph	3	0	0	5	0	0
Totals	45	8	6	41	13	10

The total incidence of spread in these 86 cases was 24 per cent, more than twice that found by clinical examination under all other methods of treatment. Spread occurred in 17 per cent of cases treated early and in 31 per cent of those treated on the fourth day or later. In this connection it is of interest that contralateral spread did not occur in a single one of our treated

experimental animals, all of which received pneumothorax within the first 48 hours¹⁹ The mortality from spread in these 86 cases was 76 per cent

It would appear that compression therapy in the first three days neither retards nor provokes extension to the opposite side Again, many more cases must be treated early and adequately before this opinion can be either confirmed or disproved

We believe that unsuccessful attempts to compress the involved lobe on lung, on or after the fourth day, increase the danger of contralateral spread If this is true, therapeutic pneumothorax is contraindicated after the first 72 hours of lobar pneumonia

Complications Empyema occurs in about 3 per cent of cases of lobar pneumonia in adults It was present in nine of the 180 adults in the pneumothorax treated group, an incidence of 5 per cent Five of these were in Blake's series His incidence was 11 per cent Blake attempts to get complete collapse as rapidly as possible, sometimes injecting as much as two liters of air at the first treatment It appears that artificial pneumothorax does not increase the likelihood of empyema unless positive pressure is deliberately produced and maintained

In this entire pneumothorax group, 17 children were treated, three by Moorman, with empyema in one and spontaneous pneumothorax in another, four by Crowell with no such complications, and 10 by Holmes and Randolph with four empyemas, three of which were accompanied by and may have resulted from spontaneous pneumothorax Holmes and Randolph's two fatal cases had empyema In each the pleural cavity was so adherent that only a small amount of air was injected under positive pressure In retrospect, the authors state that neither of these cases should have been treated

The favorable prognosis of lobar pneumonia in childhood and the increased risks of serious complications from compression therapy would seem to argue against its use in this group

Adhesions There are only two ways to find pleural adhesions in the living pneumonia patient Their presence may be inferred from the production of positive pressure and pain during instillation of air and they may be demonstrated by roentgen-ray after such injections *An amount of air more than sufficient to completely compress a pneumonic lung may be injected easily, without positive pressure and without pleural pain, and yet roentgen-ray may demonstrate adhesions which altogether prevent effective compression* Preexisting fibrous adhesions are the greatest obstacle to early effective pneumothorax therapy If this is true, it is obvious that the mathematical probability of their presence should be determined, if this is possible

Through the courtesy of Dr Krumbhaar and the Department of Pathology, records of patients autopsied at the University Hospital were placed at our disposal Consecutive protocols were examined, discarding all those which revealed any type of acute or chronic pulmonary disease except ter-

terminal bronchopneumonia The results of this survey are presented in the following table

TABLE IV

Incidence of Fibrous Pleural Adhesions in 515 Consecutive Autopsies (Acute and Chronic Pulmonary Disease Omitted Except Terminal Bronchopneumonia)

Age Group	Number of Cases	Old Adhesions	% Old Adhesions
10-19	43	10	23.3
20-29	64	29	45.3
30-39	70	26	37.1
40-49	87	42	48.3
50-59	108	55	50.9
60-69	93	55	59.1
70-79	45	23	51.1
80-89	5	2	40.0
Total	515	242	47.0

Separating the cases into decades it is apparent that from 10 to 20 years of age, old pleural adhesions are found post mortem in approximately 25 per cent of individuals dying from various causes exclusive of pulmonary disease. After the age of 20 they are present in about 50 per cent of all such cases.

How does this table tally with the presence of adhesions noted by those who have treated pneumonia by pneumothorax and tabulated this finding? Our incidence was 62 per cent, Blake's was 56 per cent, that of Holmes and Randolph 55 per cent.

Seeking an explanation for the extraordinary difference in mortality between Blake's cases treated before the end of the third day and after this time, we studied 55 autopsy records of patients dying of lobar pneumonia, paying particular attention to the type of infection, the day of death, and the pathologic changes in the pleura. While the information obtained is not sufficiently clear-cut to lend itself to statistical tabulation, the findings are of great interest. Thirty-eight per cent of these cases (irrespective of age) showed old adhesions. In addition to this, it was noted in the protocols that many of the patients dying early in the disease had fibrinous or sero-fibrinous pleurisy over the adjacent affected lobe or lobes, while many of those dying late showed fibrous pleurisy and in some there was a plastic exudate partially obliterating the pleural cavity. This was particularly true in Type III infection.

Reverting to Blake's tables which record the day on which the temperature first returned to normal, in those who recovered without complications, it is found that an artificial crisis was produced most frequently in the cases treated early. None of the patients treated after the third day had a normal temperature until several additional days had elapsed. In other words, it seems probable that during the third day, and much more frequently thereafter, recent adhesions prevent adequate compression and artificial crisis.

We firmly believe that the involved lobe or lung must be completely surrounded with air if artificial crisis is to be achieved and this can only occur

if the pleural cavity is almost entirely free Unless this treatment can provoke an artificial crisis it does no good and the patient goes on to crisis or lysis at the expected time Termination by crisis is no proof of efficacy of treatment unless the crisis is artificially induced by it In those treated early, where the pleural cavity is free, the effect is dramatic

SUMMARY AND CONCLUSIONS

The records of 197 cases of lobar pneumonia treated by artificial pneumothorax are reviewed The death rate in this group is essentially the same as general hospital mortality from this disease under all other forms of treatment We have not attempted to revise our statistics by excluding the palpably hopeless because no distinctions are drawn in compiling hospital mortality

For the reasons which we have given, we disapprove of the use of artificial pneumothorax in lobar pneumonia in children

This treatment is probably without effect on preexisting blood stream invasion but may possibly prevent late bacteremia if it is used effectively before blood stream invasion occurs

It is probable that early treatment neither increases nor decreases the usual incidence of spread There are good reasons to believe that late treatment increases the chances of its occurrence If this proves to be correct, artificial pneumothorax is contraindicated in lobar pneumonia after the third day of this disease

It does not increase the incidence of empyema in adults unless such large quantities of air are introduced that positive pressures are deliberately produced and maintained

The greatest obstacle to effective early treatment is the presence of preexisting fibrous adhesions in almost 50 per cent of adults of middle age This barrier is almost insurmountable in patients treated after the third day because the pleural reaction after this time adds new adhesions to the predictable 50 per cent already present, thus making complete compression and artificial crisis virtually impossible

Artificial crisis can only occur with a free pleural cavity, band adhesions possibly excluded, and may be expected in 50 per cent of cases treated before the fourth day This statement is predictable and is in accord with clinical experience Nothing is accomplished by compression treatment unless artificial crisis is achieved

Specific serum therapy is applicable to about 50 per cent of all patients with lobar pneumonia Artificial pneumothorax is capable of producing an artificial crisis in about the same proportion of cases and can be used in any and all types of lobar pneumonia provided the involvement is unilateral Both specific serum and pneumothorax must be used early to be effective Artificial pneumothorax properly used is a real and permanent addition to the treatment of lobar pneumonia In those cases in which artificial crisis is induced, one is privileged to witness an apparent miracle

There is never any contraindication to any other type of treatment, specific or non-specific, and the most favorable results will be achieved by the rational and coincident use of all appropriate therapeutic measures

BIBLIOGRAPHY

- 1 BLAKE, F G, HOWARD, M E, and HULL, W S The treatment of lobar pneumonia by artificial pneumothorax, *Trans Assoc Am Phys*, 1934, xlix, 119-137
- 2 BLAKE, F G Personal Communication
- 3 BEHREND, A, and COWPER, R Artificial pneumothorax in the treatment of lobar pneumonia, *Jr Am Med Assoc*, 1934, cli, 1907-1913
- 4 BEHREND, A, TUCK, V L, and ROBERTSON, W E Artificial pneumothorax in the treatment of lobar pneumonia, *Jr Lab and Clin Med* (In press)
- 5 ROBERTSON, W E Personal Communication
- 6 STOLI, H F Personal Communication
- 7 LEOPOLD, S S, and LIEBERMAN, L M The treatment of lobar pneumonia by artificial pneumothorax, *Med Clin N Am* (To be published)
- 8 MOORMAN, L J Artificial pneumothorax in treatment of pneumonia, *South Med J*, 1934, xxvii, 233-237
- 9 MOORMAN, L J Artificial pneumothorax in the treatment of pneumonia—report of cases, *Internat Clin*, 1934, iv, 119-131
- 10 ISAACS, H J, UDESKY, I C, and DE PINTO, A Pneumothorax treatment of lobar pneumonia, *Illinois Med Jr*, 1934, lvi, 267-270
- 11 HAMMOND, J J Personal Communication
- 12 CROWELL, L A, JR Pneumothorax treatment in lobar pneumonia, *South Med and Surg*, 1934, xcvi, 467-470
- 13 HINES, L E, and BENNETT, D Artificial pneumothorax in the treatment of lobar pneumonia, *Arch Int Med*, 1935, lv, 100-111
- 14 HOLMES, F G, and RANDOLPH, H Treatment of lobar pneumonia by artificial pneumothorax, *ANN INT MED*, 1935, viii, 1008-1027
- 15 DAVID, O Zur Pneumothoraxbehandlung der Lungenentzündung, *Deutsch med Wchnschr*, 1921, xlvii, 802
- 16 IBRAHIM, J, and DUKEN, J Zur Behandlung der kindlichen Pneumonie mit dem kunstlichen Pneumothorax, *Arch f Kinderh*, 1928, lxxiv, 241-249
- 17 DUKEN, J Die kunstliche Pneumothorax in der Behandlung der kindlichen Pneumonie, *Klin Wchnschr*, 1930, ii, 2195-2199
- 18 JAHR, J, and NEUMANN, R Zur Pneumothorax-Behandlung der Säuglingspneumonie, *Klin Wchnschr*, 1930, ix, 2200-2202
- 19 LIEBERMAN, L M, and LEOPOLD, S S Therapeutic pneumothorax in experimental lobar pneumonia in dogs, *Am Jr Med Sci*, 1934, clxxxvii, 315-330

AGRANULOCYTOSIS ⁺

By HENRY JACKSON, JR., M.D., *Boston, Massachusetts*

It would be impossible adequately to cover all aspects of the disease agranulocytosis in the time at my disposal. I have chosen, therefore, to attempt to clarify in so far as my knowledge of the subject permits, certain phases of the condition which are at present under dispute. Brevity necessitates a certain amount of dogmatism for which I have but little enthusiasm.

In the first place, is there such a disease entity at all? I believe there is. It is characterized by extreme leukopenia and neutropenia and occurs at all ages except early childhood. The onset is usually sudden, fever is constant and in the majority of instances ulcerative or even gangrenous lesions appear in the oral cavity, gastrointestinal tract and elsewhere. The disease runs, as a rule, a rapid course, ending in recovery or death in a short time. Much more rarely the disease is subacute or regularly recurrent. In the true condition there should be no anemia of moment, unless due to some unrelated disease, no thrombopenia, no hemorrhages into the skin or mucous membranes and the blood smear should show few, if any, immature white blood cells. There should be no lymphadenopathy not readily accounted for by adjacent sepsis nor any notable enlargement of the spleen. Unless these criteria are adhered to with some semblance of strictness, hopeless confusion results, as can readily be seen by perusal of the literature, particularly the French.

Yet leukopenia in and by itself does not make the diagnosis. I cannot emphasize this point too strongly. Leukopenia and neutropenia are common to many diseases—pancytopenia, pernicious anemia, benzol poisoning, arsenic poisoning, Kala-azar, miliary tuberculosis and certain instances of acute aleukemic leukemia. Each of these diseases has clinical and hematological characteristics which serve in most instances to identify it. Before the diagnosis of agranulocytosis is decided upon one must carefully eliminate all these. There remains what for lack of a better term may be called agranulocytosis. Mettier estimated that but 6 per cent of all leukopenias in his clinic could properly be called agranulocytosis. Doan has reached similar conclusions.

The pathological changes in the bone marrow in agranulocytosis have been so diversely described that one is left utterly bewildered and this state of affairs has served as an opening wedge for those who maintain that agranulocytosis is not a true disease, but merely a symptom complex. It is fortunate, therefore, that Klumbhaar and Fitz-Hugh and more recently Custer of Philadelphia have come forward with a clear cut and masterly description of the changes found in the true disease. From an analysis of 11 cases coming to postmortem Custer concluded that there was a marked

* Read at the Philadelphia meeting of the American College of Physicians, May 3, 1935

proliferation of the myeloblasts with a failure of these cells to mature, a view first suggested by Fitz-Hugh and Krumbhaar. The other elements of the bone marrow were undisturbed. More or less hyperplasia of the femoral marrow occurred, especially in the more chronic cases. From an analysis of 27 cases of my own coming to autopsy I have reached essentially the same conclusions and I heartily agree with Custer that the bone marrow of agranulocytosis secondary to arsenical poisoning is quite different. Certainly the bone marrow of true agranulocytosis bears no resemblance to that of pernicious anemia, aplastic anemia, or acute leukemia—all diseases which may give extreme leukopenia. Yet without examination of the bone marrow one may be unable to diagnose which of these conditions obtains.

We have then a characteristic clinical picture with a correspondingly characteristic pathological one. Such would appear to justify the cataloguing of agranulocytosis as an entity, at least until we are able to speak in terms of physiological pathology.

What then of the etiology of agranulocytosis? A few years ago there was hardly a speculation as to the cause of the disease. Now the pendulum has swung the other way and it is the fashion to incriminate amidopyrine as the most common, if not the sole, cause. There is unquestionably considerable evidence that amidopyrine may be, in at least certain cases, of etiological importance, but the *post hoc ergo propter hoc* argument is notoriously fallacious and I believe it behooves us to be cautious before drawing too broad conclusions. There is no question but that many cases of agranulocytosis follow long or massive administration of the drug. I have seen many such. But some of these very same cases recover in spite of increased administration of the same drug during the height of the illness. The drug cannot both cause and cure the disease. Furthermore, I have many instances in which there was no evidence whatever that any such drug had been taken prior to the attack. Again there are patients who have taken amidopyrine and become ill with the disease, stopped the drug completely and still had one or more relapses, and finally I have seen instances in which the attack has been apparently precipitated by amidopyrine, increased dosage of which after complete recovery has produced not the slightest change in the blood picture. It has been suggested that agranulocytosis has virtually disappeared and that this disappearance is due to the withdrawal of the drug from the market. Yet the evidence is that the sales of amidopyrine in this country were greater in the last six months of 1934 than ever before. I hold no brief for the harmlessness of amidopyrine but I must point out what I believe to be a fact—that amidopyrine has not been proved to be the sole or even the major cause of the disease. That it is of importance in certain cases I do not for a moment deny.

That an endocrine factor may be at the basis of some cases is suggested by those instances in which the onset occurs at the time of menstruation.

but I know of no work which has disclosed experimentally the nature of this endocrine abnormality

Personally I am inclined to believe that the disease agranulocytosis is of varied etiology, but there would seem to be no good reason for denying the existence of the entity on this ground alone. Pernicious anemia may be due to lack of an intrinsic factor, to radical surgical interference with the gastrointestinal tract or to malignant disease preventing the proper functioning of such factors as cause a proper maturation of the red cells. In a similar manner a variety of agents, known and unknown, may prevent proper maturation of the granular white cells and so produce the disease agranulocytosis.

Now as to the treatment of the disease. I enter this phase of the discussion with many misgivings, for it has been my lot to be responsible for one form of treatment. Certain forms of therapy, such as sterile milk, leukocytic extract and the like can be disposed of as valueless. Roentgen-ray is probably useless. When one comes to transfusions, there is less unanimity of opinion. Unquestionably cures have followed transfusion, as they have occurred spontaneously and following a large variety of remedies, but there would not seem to be convincing evidence that they are actually beneficial, and numerous authors have pointed out that following them the white count may fall even to lower levels. Personally I am decidedly against transfusions in this disease.

Pentnucleotide was introduced in 1929 and has been used with varying success by a large number of physicians all over the world. Curiously enough it would appear that in the hands of some there were rather uniformly good results, while others have had consistently poor results. The explanation of this apparent fact is not clear. Granting for the moment the premise that pentnucleotide is of value in the treatment of agranulocytosis, it is well to inquire as to the cause of such failures as have been recorded. There would seem to be two important factors. One is dosage. Again and again in the literature one finds case reports indicating that pentnucleotide was of no avail, yet careful analysis of the cases shows that but a half or a quarter or even less than the recommended amount was given. Such reports do not militate against the possible usefulness of the drug. It is generally agreed that liver extract will cure pernicious anemia, but it must be given in sufficient amounts to be effective. We recommend now that 40 c.c. pentnucleotide be given each day intramuscularly. One cannot judge its effectiveness, or lack of it, from smaller amounts. Unfortunately in certain instances fairly severe systemic reactions occur, so it is well to start with smaller amounts before proceeding to the larger, and in some instances full amounts cannot be given at all. It is useless, however, to give small infrequent amounts.

Further, it must be recognized that agranulocytosis is often a fulminating disease and that complete absence of granulocytes for more than a relatively short time is probably incompatible with life. In spite of adequate

dosage of a theoretically potent drug, therefore, a patient may die before the beneficial results accrue

The second factor in the apparent failure of pentnucleotide in certain cases would appear to be improper diagnosis. As Custer says, the diagnosis of agranulocytosis can often be negated by a glance over the clinical records. There has never been any claim that pentnucleotide will cure acute leukemia—even in the aleukemic stage—yet the clinical differential diagnosis between aleukemic leukemia and agranulocytosis may be fraught with the greatest difficulty. There has never been any claim that pentnucleotide will cure aplastic anemia or pernicious anemia, yet many times, particularly in the foreign literature, instances of accompanying leukopenia in these diseases have been labelled agranulocytosis and treated as such. Again I would emphasize that leukopenia in and by itself is no criterion for the diagnosis of agranulocytosis. If we grant the existence of a disease entity we must confine our therapeutic aims to this entity before deciding on their merits.

Liver extract has recently been suggested as a cure for agranulocytosis. There is no question that cures have followed its use, but if such sequence of events be regarded as evidence of the effectiveness of the drug in this disease, how many more data have we on this score alone? Furthermore, many of the cases reported as cured by liver extract are obviously pernicious anemia with extreme leukopenia. Of this there can be no doubt. Bonsdorff treated two cases with liver intravenously with recovery in both instances. There seems to be no reason to doubt, however, that the first patient was suffering from pernicious anemia. She had a red blood cell count of 528,000 per cu mm, a color index of 1.32 and a white count of 1,750. His second patient had extreme leukopenia apparently due to novarsenobenzol and bismuth. The withdrawal of these drugs may well have had as beneficial an effect as the liver extract. Bonsdorff argues that because the white count rises in pernicious anemia following liver therapy it should also rise in agranulocytosis. Yet the mechanism of the leukopenia of pernicious anemia is as yet not clear. It may well be that it is similar to that which produces the anemia in leukemia, namely a crowding out of one series of cells by the overgrowth of another. If this be so, liver therapy would cause a rise of the white blood cell count in pernicious anemia by an indirect rather than a direct method. At present the ultimate value of liver therapy in agranulocytosis cannot be estimated. It can only be said that a few patients have been successfully treated. There would appear to be less evidence for the effectiveness of liver extract than there is for pentnucleotide. Either the one or the other, or neither, may ultimately prove to be of value. At present a larger number of cures have followed pentnucleotide than any other form of therapy, but the drug must be given in the correct dosage to the correct disease.

One author has suggested that the sole hope for the granulopenia patient is sepsis. I can only say that that hope is all too often fulfilled. That sepsis raises the white count in the presence of a normal bone marrow is no

evidence that it will or can stimulate a paralyzed bone marrow to activity. One of my cases developed agranulocytosis in the midst of an attack of boils. It would be far better in my opinion to do all we can to avoid infection.

It appears to me that at present the best method of treating true agranulocytosis is by intelligent nursing care, adequate fluids and food, the careful avoidance of sepsis, if possible, and the administration of full doses of pent-nucleotide. Such imperative surgical measures as would be instituted in patients with a normal blood should be used fearlessly in agranulocytosis. Codeine is the best sedative. The future only will tell whether this régime is the most effective. It may well be that some other drug will be found far more effective.

CYCLICAL AGRANULOCYTIC ANGINA¹

By D J STEPHENS, M D, and JOHN S LAWRENCE, M D,
Rochester, New York

ALTHOUGH Franke¹ in 1930 was able to find only three instances of the recurrence of attacks of agranulocytic angina, there are at the present time numerous reports of this condition in the literature. In a few instances these episodes of agranulocytosis have been cyclical in character^{2, 3, 4, 5, 6}. One of these cyclical cases⁶ has had recurrences simultaneously with the menses. During the past two years we have had under constant observation a patient who has presented this unusual picture of recurrences of granulocytopenia with each menstrual period. A brief report of the main findings in this patient has been made previously⁷. The purpose of this paper is to give the results of our studies of this patient in more detail in the hope that the data may be of some use in the further study of this disease of obscure etiology.

CASE REPORT

Mrs G K, a 38 year old, white widow was observed in her first attack of granulocytopenia in November 1932. She had previously been seen on several occasions in the Out-Patient Department because of symptoms of mild hypertrophic arthritis and repeated attacks of urticaria and migraine. In February 1930, she had been admitted to the hospital because of an especially severe attack of urticaria. She gave a history of having taken daily doses of aspirin or amidopyrine for headache for several weeks. It is of interest that at this time, the total white blood cells numbered 7600 per cu mm, with differential formula as follows: Polymorphonuclear neutrophils 65 per cent, lymphocytes 33 per cent, monocytes 2 per cent. Skin tests for a number of foods and other substances, including amidopyrine, acetylsalicylic acid and neocinchophen were uniformly negative. In September 1931, cholecystectomy was done because of chronic cholecystitis and cholelithiasis. At this time the white blood cell count was 8600 per cu mm, with the following differential leukocyte formula: polymorphonuclear neutrophils 73 per cent, lymphocytes 19 per cent, monocytes 7 per cent, eosinophiles 1 per cent. During the following year she remained well except for frequent headaches (migraine) and dysmenorrhea, for which she took amidopyrine, acetylsalicylic acid and sodium amylal. The exact dosage and frequency with which these were used is not known.

On November 3, 1932 the patient was again admitted to the hospital. Six days before, during the menstrual period, there had been sudden onset of an acute illness, characterized by chills, fever, headache, malaise, anorexia and sore throat. On examination she appeared to be acutely ill. The temperature was 37.5° C, pulse 90, respirations 20. The pharynx was diffusely reddened and edematous. Cervical lymph nodes were moderately enlarged. There were no other physical findings of significance. Throat culture showed a mixed flora with 20 per cent *Streptococcus hemolyticus*. The urine showed no abnormalities. Blood counts on admission were

* Received for publication February 18, 1935.

From the Department of Medicine, University of Rochester School of Medicine and Dentistry and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, New York.

as follows red blood cells 3,850,000 per cu mm, hemoglobin 11.0 gm per 100 c.c. of blood, white blood cells 2000 per cu mm. Of the latter, 14 per cent were polymorphonuclear neutrophils, the remainder non-granular cells. Local treatment of the throat was instituted and daily injections of pentnucleotide K-96 were begun. During the first three days in the hospital the temperature varied between 37° and 38.5° C. By November 9 the temperature had returned to normal and the throat symptoms had subsided. At this time the leukocytes numbered 6800 per cu mm of which 59.5 per cent were neutrophils. Leukocyte counts during this attack and during the following two years are shown graphically in figure 1.

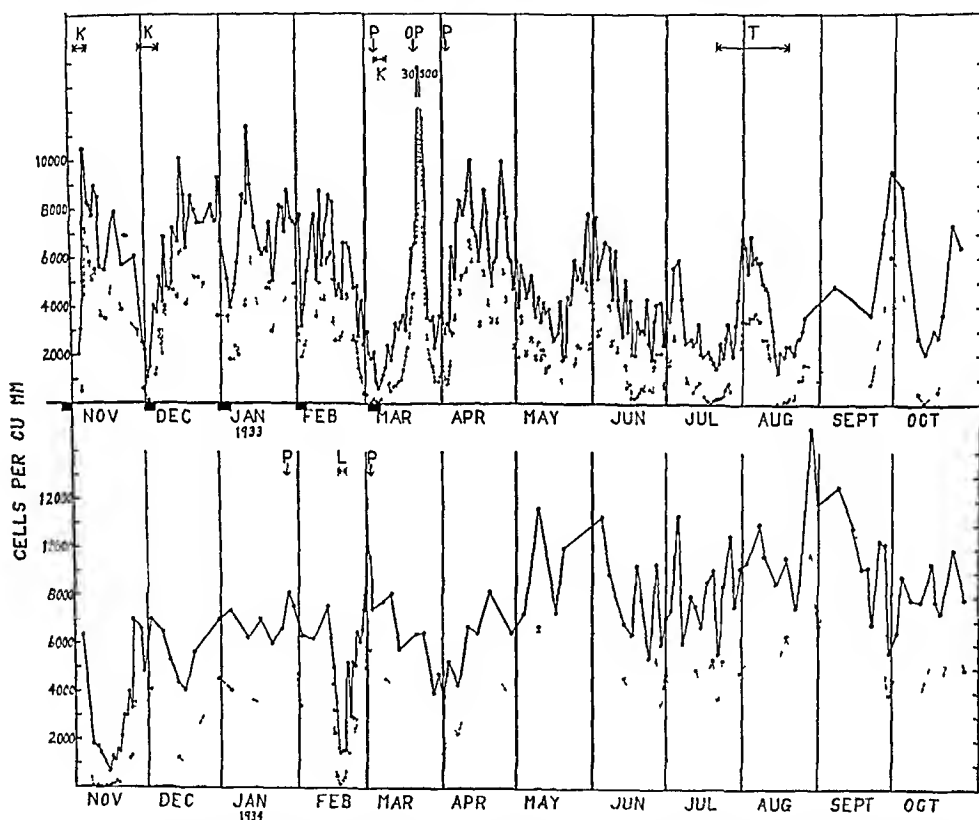


FIG 1 Solid line total leukocytes Broken line neutrophils The areas blocked in black represent the menstrual periods K—pentnucleotide K-96, 20 c.c. daily intramuscularly P—amidopyrine, five grains by mouth OP—bilateral salpingo-oophorectomy T—theelin L—Lederle's parenteral liver extract, 6 c.c. daily intramuscularly

On November 29, two days before the onset of the menstrual period, the patient was again admitted to the hospital because of a decreasing leukocyte count. At this time the white blood cells numbered 2900, with 19 per cent granular cells. There were no symptoms with the exception of fatigue which was attributed to overwork. Pentnucleotide was again given in doses of 10 c.c. intramuscularly twice daily and continued for eight days, at the end of which time the leukocyte count was normal. On December 7, a biopsy of sternal bone marrow was obtained. The bone marrow appeared to be essentially normal, except for an apparent decrease in the number of megakaryocytes. There was an abundance of myeloid cells in all stages of development.

In the middle of December, the patient developed a furuncle of the left nostril, slight swelling of the left side of the face and a tender, enlarged lymph gland in the

left anterior cervical region. During this infection, which subsided in a few days the leukocyte count remained normal. During the next two months there were no complaints. There were, however, two periods of leukopenia during which the total leukocyte count was less than 4000 per cu mm, the total granulocytes less than 2000 per cu mm. Each of these episodes occurred at the time of the menstrual period.

During the last 10 days in February 1933, there was a mild upper respiratory infection, with gradual decrease in the leukocyte count. On March 4, the total white blood cell count had dropped to 900 per cu mm with 1 per cent granulocytes. In addition to rhinitis, there was herpes labialis, with swelling, redness and tenderness of the upper lip. The menstrual period had begun the day before. Pentnucleotide was again given. During the next two weeks there was a gradual increase in the number of granulocytes and subsidence of the infection.

At this time the patient had been under observation for five months. With each of five menstrual periods, there had been an attack of neutropenia. Three of these had been of sufficient severity to require admission to the hospital. After much discussion it was decided to induce menopause by surgical procedures. Accordingly, on March 21, 1933, subtotal hysterectomy and bilateral salpingo-oophorectomy were done by Dr. Karl Wilson. On the morning of the operation the white blood cell count was 9600 per cu mm with 81.5 per cent granulocytes. Six hours after operation, the total leukocytes had increased to 30,500 per cu mm, of which 93.5 per cent were granulocytes. During the next few days, however, there was a precipitous diminution in the total leukocytes and granulocytes. For several days the granulocytes varied between 800 and 1500 per cu mm. During this time the patient was making an otherwise uneventful recovery from the operation. Microscopic examination of the ovaries showed a relatively large number of corpora fibrosa and an unusual persistence of old corpora lutea. During the period from March 12 to April 15, 1933 the urine was examined daily by Dr. C. A. Elden for the presence of estrin by a method previously described.⁸ During the 10 days before operation the 24-hour urine specimens contained an average of about 25 rat units of estrin, for 25 days after operation the average content was 5 to 10 rat units. During this period there were two cycles of neutropenia. There was no apparent relationship between the leukocyte count and the amount of estrin excreted in the urine. Extracts of the patient's urine showed a positive ovulation test on the twenty-second day and on the sixty-second day after operation.

During the next few months there were recurrent periods of neutropenia of varying severity at approximately monthly intervals (figure 1). With the majority of these there were no evidences of infection and admission to the hospital was not necessary during this period. Many of the attacks of neutropenia were, however, accompanied by fatigue, irritability, some general malaise and on a few occasions slight soreness of the throat. The moderate degree of anemia that was present during the early months of observation had been relieved by large doses of iron by mouth. The hemoglobin and red blood cell levels have since remained within normal limits.

For several months after operation there were menopausal symptoms, chiefly in the nature of frequent "hot flashes." Between July 20 and August 3, theelin was administered in daily doses of 3 cc intramuscularly. From August 3 to 18 the daily dose of theelin was 2 cc. During the period of theelin administration there was partial relief of menopausal symptoms but there was no apparent effect on the neutropenic cycle.

On November 13, 1933, it was again necessary to admit her to the hospital because of fever, prostration, and marked soreness of the throat and gums. The throat was beefy red, there was marked gingivitis, moderate enlargement and tenderness of the cervical lymph nodes and an inflamed, tender, thrombosed hemorrhoid. The white blood cell count dropped to 600 per cu mm and granulocytes disappeared.

entirely from the peripheral blood. Because of the severe reactions which attended the injections of pentnucleotide in three previous attacks in which it had been given, and in view of the fact that spontaneous recovery had resulted from other periods of severe neutropenia, nucleotide was not given. Treatment was limited to local and symptomatic measures. There was gradual increase in the total leukocytes and granulocytes and the manifestations of infection subsided.

In December, there was a period of moderate neutropenia without symptoms. Throughout January 1934 the white blood cell count remained at a normal level, although there was a moderately severe respiratory infection during the latter part of the month. During February, however, sore throat, gingivitis, herpes and fever again appeared and were accompanied by a decrease in the total leukocyte count to 1450 per cu mm with 10.5 per cent granulocytes on the seventeenth. During the next three days Lederle's Liver Extract was given intramuscularly in doses of 6 c.c. daily. Again the leukocyte count rose and the symptoms disappeared.

During the first week in March 1934, the patient was requested to omit medicines of all kinds with the exception of codeine, which was necessary for the control of headache. This restriction has been maintained since that time. During the latter part of March there was a decrease in the white blood cells and granulocytes with subsequent gradual increase during the early part of April. Since that time the leukocyte level and the percentage of granulocytes have been within normal limits and the patient has remained well except for occasional headache.

During the two year period from November 1932 through October 1934, we have observed in this patient 11 periods of severe granulocytopenia, five of these were accompanied by fever, lymphadenopathy and evidences of infection of the upper respiratory tract. Symptoms during the other six periods were limited to malaise, fatigue, irritability, and slight sore throat. In addition there were five symptomless periods of less severe granulocytopenia, during which the total number of granulocytes was reduced to a level varying between 1000 and 2000 per cu mm. Throughout the period from January 1930 to March 1934, frequent doses of amidopyrine and other analgesics and sedatives were taken. On four occasions, amidopyrine was administered to the patient during observation in the hospital (figure 1). No significant change occurred in the trend of the leukocyte level at these times. At least one neutropenic cycle (in March-April, 1934) occurred without antecedent drug ingestion.

Throughout the two year period of observation, during which approximately 400 differential leukocyte counts of 200 cells each were made, eosinophiles were observed in the differential formula on only two occasions. Basophiles and monocytes were present in small numbers during this period, the relative number of lymphocytes varied inversely with the number of neutrophils.

DISCUSSION

We felt justified in having a bilateral salpingo-oophorectomy performed for the following reasons. First, the patient was a widow with one child and had no desire for marriage and other children. Second, her age was such that the menopause would occur normally within a few years. Third, the exact coincidence of the menstrual cycle and the period of granulocytopenia on repeated occasions was so striking that it seemed reasonable to assume that there *might* be some causal relationship even though similar cyclical recurrences had been observed in the male³. Fourth, the patient was perfectly willing to have the operation performed as an experiment.

The effect of the oophorectomy is difficult to evaluate. Cyclical recur-

rences were present for one year after operation. However, the general shape of the curves representing the total number of white blood cells and the absolute number of neutrophils in the blood stream underwent some changes during this period. On the whole, the average total number of cells was less and so far as this goes suggested that granulopoiesis was inhibited by this operation. Nevertheless, after this postoperation period of one year there has been no recurrence for 10 months. The question naturally arises as to whether the omission of amidopyrine was responsible for the disappearance of the recurrences. We cannot answer this. Certain it is that amidopyrine was taken at repeated intervals during the period of recurrences without any demonstrable effect on the white blood cell picture. It is unfortunate that we have no accurate record of the amount of this drug that was taken at various times. In view of the many reports in the literature since the original papers by Watkins⁹ and Madison and Squier¹⁰ suggesting a close relationship between the drug and granulopenia we have been unwilling to give amidopyrine to this patient. We do not feel, however, that the evidence *in this case* justifies any statement to the effect that this chemical agent was the responsible factor. In this connection, Jackson's¹¹ recent report of the absence of ingestion of pyramidon or related drugs in 44 per cent of his series of cases is of interest.

In connection with the feeling of certain investigators¹² that allergy is a strong factor in these cases, there is confirmatory evidence to be found in the fact that she has suffered from extreme generalized urticaria in the past. Against this idea is the almost total absence of eosinophiles from the peripheral blood of this patient throughout her entire course of illness.

In regard to therapy, we find little evidence in this one patient of any benefit from either pentnucleotide or liver extract. It is true that the periods of granulopenia were of shorter duration and that recovery from them was associated with the presence of more myelocytes in the peripheral blood when one or both of these substances were administered intramuscularly. However, these findings represent no greater variations from the usual response of such patients than one would expect to find in untreated cases.

Our results with regard to the urinary output of the female sex hormone and of an anterior pituitary-like substance are of some interest. In contrast to the findings of Thompson⁵ we found absolutely no correlation between the level of the white blood cell count and the number of rat units of female sex hormone secreted in the urine. Prior to oophorectomy our values were within normal limits (approximately 25 to 26 units daily) at a time when there was well marked granulopenia. Following operation these values dropped to approximately 5 to 10 units daily and remained there even when neutropenia was present. These findings would seem to indicate that the white blood cell picture was independent of the ovarian hormone resulting from follicular activity. Further confirmatory

evidence of this is found in the failure of theelin to produce any change in the white blood cell picture. The results of the repeated determinations of the amount of anterior pituitary-like substance in the urine give only slight room for speculation. The most that can be said in this connection is that a positive test was found at an earlier postoperative date than is usual. That these findings point to any positive connection between this substance and the white blood cell picture, is open to considerable question.

The histological changes in the ovaries of this patient were of the same character as those seen in the ovaries of monkeys following the administration of large quantities of anterior pituitary-like hormone (prolan). In view of this we studied the white blood cell picture of two monkeys for two months while they were receiving 10 c.c. antuitrin S (Parke, Davis and Company) daily subcutaneously. No change in the white blood cell formula was demonstrable.

In order to determine whether menstrual periods in normal young women were associated with any comparable changes in the blood picture, we have investigated the total and differential white blood cell counts of six normal young women over a period of two months including two menstrual cycles. No variation greater than normal was present in the white blood cell counts of these individuals. These findings are in accord with those of Smith and McDowell.

The bone marrow findings are of interest since they presented a normal picture. What they would have been at the time of granulopenia we do not know. In this connection, it is of interest that this patient was able to respond to operation by the usual postoperative leukocytosis. This ability to respond normally to stimuli to white blood cell formation at periods after the subsidence of acute granulopenia has been noted previously^{1,13}

SUMMARY

The findings in a patient with agranulocytic angina manifested by recurrences at the time of the menstrual cycles have been reported. Following bilateral oophorectomy there was slight change in the picture during a period of one year, after which time no further recurrences occurred.

Anidopyrine was taken at times by this patient but our data do not allow any positive statement as to any causal relationship between it and the cycles of granulopenia.

BIBLIOGRAPHY

1. FRANKE, O. Über rezidivierende Agranulozytose, *Folia haemat.*, 1930, *vi*, 419-426.
2. LEALE, M. Recurrent furunculosis in an infant showing an unusual blood picture, *Jr Am Med Assoc.*, 1910, *liv*, 1854.
3. RUTLEDGE, B. H., HANSEN-PRUSS, O. C., and THAYER, W. S. Recurrent agranulocytosis, *Bull Johns Hopkins Hosp.*, 1930, *xlvi*, 369.
4. DOAN, C. A. Neutropenic state, its significance and therapeutic rationale, *Jr Am Med Assoc.*, 1932, *xcix*, 194-202.

- 5 THOMPSON, W P Observations on possible relation between agranulocytosis and menstruation with further studies on case of cyclic neutropenia, N E Jr Med, 1934, ccx, 176-178
- 6 JACKSON, H, JR, and MERRILL, D A Agranulocytic angina associated with the menstrual cycle, N E Jr Med, 1934, ccx, 175-176
- 7 STEPHENS, D J, and LAWRENCE, J S Recurrent agranulocytosis, Jr Clin Invest, 1934, xiii, 711
- 8 ELDEN, C A Method of study and treatment of menstrual disturbances of endocrine origin, Am Jr Obst and Gynec, 1934, xxviii, 179-186
- 9 WATKINS, C H The possible role of barbiturates and amidopyrine in causation of leukopenic states, Proc Staff Meetings Mayo Clinic 1933, viii, 713-714
- 10 MADISON, F W, and SQUIER, T L Primary granulocytopenia after administration of benzene chain derivatives, Central Society for Clinical Research, 6 Annual Meeting, Chicago, Oct 27, 28, 1933 Reported in Jr Am Med Assoc, 1933, ci, 2076
- 11 JACKSON, H, JR Relation of amidopyrine and allied drugs to etiology of agranulocytic angina, Am Jr Med Sci, 1934, clxxxviii, 482-486
- 12 SCHILLING, V The blood picture and its clinical significance, 1929, C V Mosby Co, St Louis, p 197
- 13 HARKINS, H Granulopenia and agranulocytic angina, Jr Am Med Assoc, 1932, xciv, 1132-1138

THE ETIOLOGY AND PREVENTION OF ANEMIA IN PREGNANCY¹

By MAURICE B STRAUSS, M D , *Boston, Massachusetts*

PREGNANCY may be a coincidence in the course of any number of conditions which in themselves cause anemia, such as leukemia, hemolytic jaundice, and chronic blood loss. Furthermore the gravid state may in part be responsible for hemorrhage, pyelitis and puerperal sepsis, each of which may contribute to the development of anemia. Disregarding patients with anemia due to such well recognized causes, there remains a large group of women who during pregnancy develop moderate to severe anemia which has no obvious etiology. Two kinds of such anemia are encountered. One type, hypochromic in character, occurs much more frequently than the second type which is macrocytic, or "pernicious" in morphology.

Hypochromic anemia in non-pregnant individuals is generally believed to be due to a nutritional deficiency. This deficiency may result from a direct dietary lack, or from faulty absorption due to gastrointestinal abnormalities, or from a loss of blood-building materials, as for example, in chronic bleeding. Not infrequently a combination of two or all three of these factors is encountered in any given case.

When women suffering from these defects become pregnant, not only may a preexisting anemia be much enhanced but severe anemia may develop. In the hypochromic anemia of pregnancy there is seldom significant alteration in leukocytes or blood platelets, but stained films show small pale erythrocytes. The chief presenting clinical symptoms are pallor, lack of a sense of well being and excessive fatigability. In the very severe cases edema, dyspnea, prostration and syncope may be observed. Rarely is enlargement of the spleen detected.

Thirty patients with this type of anemia in pregnancy were studied,¹ all of whom had severe anemia, with less than 45 per cent hemoglobin (Sahli) (7.02 gm per 100 cc). Rigorous examination failed to reveal concomitant disease or loss of blood. Seventeen of the 30 patients had complete posthistamine gastric anacidity, even when examined after parturition. Ten patients had little or no free hydrochloric acid in the gastric secretion after the usual alcohol test meal, and diminished amounts after histamine stimulation. Two patients only had normal gastric acidity post partum.

With but one exception, all the patients who did not have complete gastric anacidity had partaken of diets poor in iron, not only throughout pregnancy but often over a period of years. Eight of the 17 patients with complete absence of gastric free hydrochloric acid had partaken of good, if not op-

* Read at the Philadelphia meeting of the American College of Physicians, May 2, 1935.
From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital, and the Departments of Medicine and Tropical Medicine, Harvard Medical School, Boston, Massachusetts.

timal, diets throughout pregnancy, while the remainder had not had an adequate intake of iron-containing foods. It was thus apparent that either gastric secretory defects or diets deficient in iron-containing foods, or both these factors, were present in the patients with hypochromic anemia developing in pregnancy. Recently Davies and Shelley² have made a similar study of hypochromic anemia in pregnancy. Two of their 20 patients had normal gastric acidity, the other 18 having hypoacidity or anacidity. Deficient diets were encountered in 14 of the 20 women.

Furthermore it is to be remembered that all of these women had what to them was essentially comparable to chronic blood loss, since the building stones for the fetal hemoglobin are of necessity derived from the maternal organism.³ No matter how anemic the mothers became, in every instance their infants were born with a normal red blood cell count and a normal amount of hemoglobin.¹ The materials entering into the formation of the fetal hemoglobin are just as certainly lost to the mother as if there were menorrhagia.

The treatment of hypochromic anemia in pregnancy does not differ from the treatment of this condition in non-pregnant patients. Iron in adequate dosage (6 gm of ferric ammonium citrate or 1 gm of ferrous sulphate daily in our experience) has resulted in prompt recovery from the anemia in every instance.¹ Hemoglobin is regenerated in the severe cases at a rate of approximately 1 per cent (0.156 gm per 100 cc) per day, irrespective of whether treatment is instituted during or after pregnancy.

The prevention of this type of anemia in pregnancy may probably be accomplished, in the absence of gastrointestinal disturbances, by supplying the pregnant woman with a diet adequate in blood-building materials. A study which is now being carried out⁴ indicates that hypochromic anemia may be uniformly prevented by the administration of small doses of ferrous sulphate (0.4 to 0.6 gm) daily, to pregnant women. In a series of 100 normal pregnant women so treated anemia has not developed, whereas a significant degree of hemoglobin reduction has occurred not infrequently in a control series of 100 normal pregnant women studied under the same conditions as the first group but not given iron.

The prevention and treatment of this form of anemia in pregnancy is important, not only from the viewpoint of the health of the mother, but also that of the child. Although the infants born to women suffering from hypochromic anemia of pregnancy show no reduction in the number of red blood cells or the percentage of hemoglobin at birth, they ordinarily develop hypochromic anemia during their first year of life.³ This is presumably due to a failure on the part of the fetus to store an adequate amount of blood-building materials during its intra-uterine existence. During that period of neonatal life when its diet is usually restricted to milk, the normal infant draws upon its large supply of iron stored in the liver and other organs, which is probably lacking in infants born of women who are themselves deficient in iron. If, however, the anemic mother is

given sufficient iron before delivery so that her hemoglobin approaches the normal range at or before parturition, hypochromic anemia due to deficient iron storage does not develop in her infant³

Patients with macrocytic or "pernicious" anemia of pregnancy are usually more seriously ill than those with hypochromic anemia. In addition to the symptoms referable to anemia per se, nausea, vomiting and diarrhea are common. Fever, without demonstrable infection, abating when specific anti-anemic therapy is employed, occurs in most cases. Soreness of the tongue, splenomegaly and neural signs are occasionally encountered. Gastric anacidity or hypoacidity occurs in about 50 per cent of cases.

The examination of the blood shows that the number of erythrocytes is more markedly diminished than the amount of hemoglobin so that the color index is usually above 1. Moderate variation in size and shape of the red blood cells on stained blood films is the rule. Macrocytes, microcytes and tailed forms are frequent. Megaloblasts are rarely seen except in the early stages of remission.

Mean corpuscular volume determinations show a somewhat increased cell size (from 105 to 130 cubic microns), on the average not so marked as in Addisonian pernicious anemia. The concentration of hemoglobin in the red blood cells is frequently slightly reduced. The leukocytes and blood platelets are either normal or slightly decreased. A relative increase of lymphocytes accompanies the leukopenia in most cases. The serum color is either normal or slightly more yellow than normal.

There is evidence which suggests that this anemia is a manifestation of the same kind of nutritional deficiency state as exists generally in anemias of the pernicious type. Studies of these patients have shown that the same etiologic mechanisms produce this type of anemia in pregnancy as are active in non-pregnant patients. Certain of the women apparently develop the deficiency state as a result of inadequate diet alone⁵, in others a virtual deficiency develops because of a lack of Castle's "intrinsic factor" of the gastric juice¹, and in many there is reason to believe that a combination of both these causes is responsible¹. Clear-cut evidence pointing to defective absorption as an etiologic factor in this type of anemia in pregnancy is lacking, but it seems probable that this is involved in certain cases.

Macrocytic (pernicious) anemia of pregnancy may be relieved by the administration of materials potent in Addisonian pernicious anemia. When treatment is instituted during pregnancy much larger doses of potent material than are usual in the average case of Addisonian pernicious anemia may be required. For patients who do not respond readily to potent material administered orally, liver extract should be injected. Daily injections of as much as 5 to 10 cc of Solution Liver Extract Lilly (N N R) have been required in certain cases in order to produce remission.

SUMMARY

1 The hypochromic anemia of pregnancy is due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoaeridity or associated gastrointestinal defects in the presence of the fetal demand for blood-building materials. It may be completely relieved, either during or after pregnancy, by the administration of iron in suitable (usually large) doses.

2 The macrocytic anemia of pregnancy may be due to a temporary lack in the gastric juice of a specific intrinsic factor, to direct dietary deficiency, or to a combination of these factors. It may possibly result at times from disturbances of intestinal absorption. It can be relieved either during or after pregnancy by the administration in adequate dosage of materials potent in Addisonian pernicious anemia.

3 The development of anemia in pregnancy may best be prevented by supplying the pregnant woman with an adequate intake of blood-building materials.

BIBLIOGRAPHY

- 1 STRAUSS, M. B., and CASTLE, W. B. Studies of anemia in pregnancy, III, *Am. Jr. Med. Sci.*, 1933, *clxxx*, 539-551.
- 2 DAVIES, D. T., and SHIFFRIN, U. Some observations on hypochromic anaemia and its relation to pregnancy, *Lancet*, 1934, *ii*, 1094-1099.
- 3 STRAUSS, M. B. Anemia of infancy from maternal iron deficiency in pregnancy, *Jr. Clin. Invest.*, 1933, *xii*, 345-353.
- 4 Dr. John C. Corrigan, Boston.
- 5 WILLS, L. Treatment of "pernicious anaemia of pregnancy" and "tropical anaemia" with special reference to yeast extract as curative agent, *Brit. Med. Jr.*, 1931, *i*, 1059-1064.

A STUDY OF NINE CASES OF BRONCHOMONILIASIS^{*}

By JOHN W. FLINN, M.D., F.A.C.P., ROBERT S. FLINN, M.D., F.A.C.P.,
and ZEBUD M. FLINN, M.D., *Prescott, Arizona*

MONILIA may be regarded physiologically as true yeasts since they too ferment sugars with the production of gas. Morphologically, however, they differ from true yeasts (*Saccharomyces*) in that they have a vegetative body (mycelium), consisting of a collection of fine filaments or threads (hyphae) and reproduce by free-born spores (conidia). True yeasts have no definite mycelium and they reproduce by ascospores. Consequently the genus, *Monilia* Persoon is very generally placed in the class, *Fungi imperfecti* (Hyphomycetes). It is further classified in the family *Oosporaceae* Saccardo, as its spores are arranged in chain-like formation. Further morphological differentiation has not been made and classification into genus and species is based on biochemical reactions in fermenting sugars.

Bronchomoniliasis is a disease of the respiratory tract caused by any species of the genus *Monilia*. The first reported case was by Castellani from Ceylon in 1905. Boggs and Pincoffs of Baltimore reported the first case in the United States in 1915. A review of medical literature in 1931 showed only 11 additional reports in the United States up to that time. None of our cases are included in these figures.

The first case we recognized was referred to us in January 1924, from Wheeling, West Virginia, with a diagnosis of advanced pulmonary tuberculosis. Repeated examinations of the sputum were negative for tubercle bacilli and we made a tentative diagnosis of unresolved pneumonia. Several months later while culturing the sputum for an autogenous vaccine we, quite by accident, stumbled on some yeast cells on a neglected plate of culture medium. These yeast cells were subcultured and later classified by their morphology, their cultural characteristics and biochemical reactions in the genus *Monilia*.

In the meantime these microorganisms were injected into the lungs of rabbits and produced typical lesions, which will be referred to later. Cultures from these lesions showed an organism with the same characteristics and chemical reactions as those isolated from the patient's sputum. We therefore felt justified in making a definite diagnosis of bronchomoniliasis.

We then issued strict orders in our laboratory that a thorough search for fungi, including cultural study, be made on any sputum in which repeated examinations failed to show tubercle bacilli. In this way we have since picked up eight other cases of uncomplicated bronchomoniliasis, which otherwise would probably have been overlooked. The same diagnostic methods were followed as in case 1.

^{*} Read at the Chicago meeting of the American College of Physicians, April 20, 1934

It was not until 1933 that we began to determine with what species of *Monilia* we were dealing. Further study of their biochemical reactions in fermenting sugars enabled us to classify the microorganisms in our last two cases in the species *Monilia Pinoyi*. One of these cases came to autopsy and the same species of monilia was recovered from the pleural fluid, lungs and brain. Autopsy findings are reported later.

CLASSIFICATION

Table 1 shows the classification of microorganisms that we have tentatively adopted. It follows somewhat closely that suggested by Castellani, and seems to us the most practical classification obtainable at present. Its general principles were indicated in our opening paragraph.

TABLE I

Classification of Microorganisms

	Thallophyta (thallus)	Spermatophyta (seed)	Psidophyta (fern)	Byrophyta (moss)
Subdivisions	Fungaceae (saprophytic and parasitic)	Algae (chlorophyll)		
Divisions	Fungi (higher)	Bacteria (lower fungi)	Vegetative bodies	
Class	Eumycetes (fungi found in man, filamentous forms, single nuclei)			
Order	Fungi imperfecti (Hyphomycetes) yeast-like fungi, free born spores			
Suborder	Thallosporales (thallus reproduction, mycelial hyphae)			
Family	Blastosporinae (asexual, oval budding forms)			
Genus	Oosporaceae Saccardo (formation of chain-like spores)			
Species	<i>Monilia Persoon</i> (sugar fermentations, gas formation, budding forms in culture)			
	<i>Monilia Pinoyi</i> (sugar reactions, pathogenicity to animals)			

MYCOLOGY

Figure 1, a, b, c, d, shows photomicrographs of cultures of *Monilia Pinoyi* at different periods of growth. Figure 1a (48 hours) shows yeast-like fungi with budding forms (class, Fungi imperfecti). In figure 1b (3 days) we see beginning division of the free-born spores. Figure 1c (5 days) shows the formation of mycelial hyphae (order Thallosporales). Figure 1d (15 days) shows the formation of chain-like spores (family Oosporaceae Saccardo) and mycelial hyphae.

Table 2 shows the further classification of these organisms into the genus *Monilia Persoon* by their ability to ferment glucose and form gas and finally into the species *Monilia Pinoyi* by their sugar reactions and pathogenicity to laboratory animals.

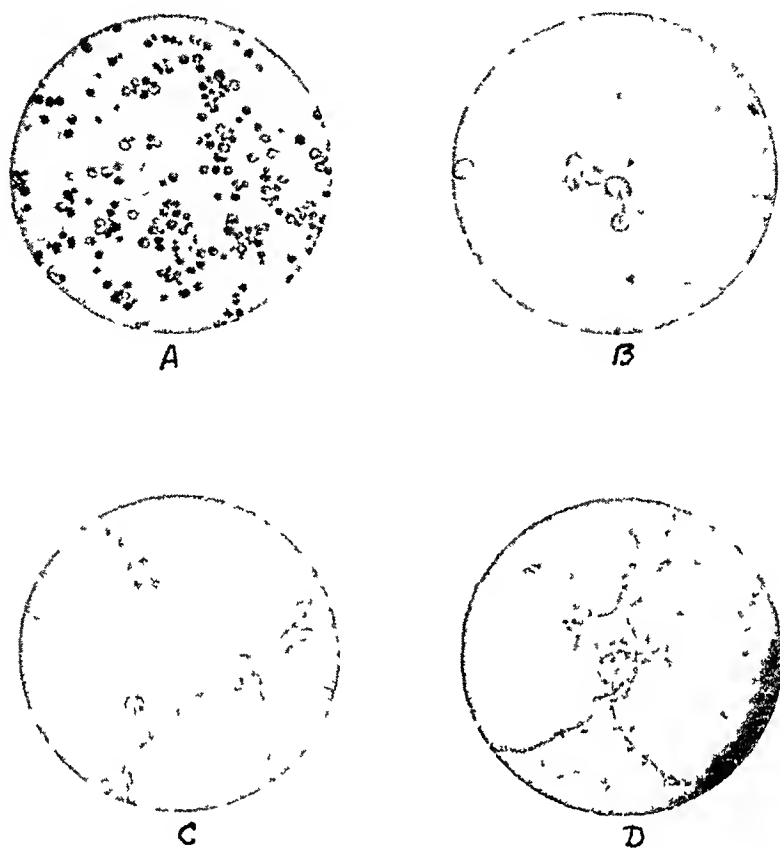


FIG 1 Cultures of *Monilia Pmoyi* (a) Forty-eight hours' growth showing yeast-like fungi with budding forms (b) Three-day growth showing beginning division of the free-born spores (c) Five-day growth showing the formation of mycelial hyphae (order Thallosporales) (d) Fifteen-day growth showing the formation of chain-like growths (family Oosporaceae Saccardo)

LABORATORY DIAGNOSIS

Monilia may be found very frequently in the normal mouth and throat so that the mere presence of *monilia* in sputum is not sufficient evidence to establish a diagnosis of bronchomoniliasis. Precautions should be taken to prevent contamination of the sputum from an outside source and the mouth and throat should be cleansed by gargling before collection of sputum.

A positive diagnosis of bronchomoniliasis is justified only by the constant finding of a pathogenic *monilia* species in the expectorated sputum. The pathogenicity of the organisms and their causative relationship to the disease in question can be proved only when their intra-pulmonary inoculation in rabbits results in the production of small pulmonary nodules. Microscopically, these nodules show a picture seen in other species of granulomatous processes and consist of leukocytes, epithelioid and giant cells.

TABLE II
Subclassification into Genus and Species

[illegible]

with or without a central area of necrosis. The periphery is usually composed of fibroblastic elements. In addition to these tubercles there may be present a generalized hyperemia throughout the affected pulmonary tissues, associated with a parenchymatous and interstitial edema of the alveolar epithelium and a narrowing of the alveolar tubules. Monilia must be recovered from these lesions.

CLINICAL DIAGNOSIS

Symptomatology Table 3 summarizes the outstanding symptoms in our nine cases. The age varied from 21 to 58 with an average of 35.5 years, confirming the observations of others that most cases occur in adults. The cases were almost equally divided between males and females. The duration of the disease had been from four to seven years in four cases and from four months to two years in five cases. The onset was influenzal-like in five cases. Pleurisy was the initial symptom in three cases. In the one remaining case the attack began with an hemoptysis. Severe cough was a prominent symptom in the majority of cases, being paroxysmal in character and especially troublesome at night.

In general there was nothing characteristic about the expectoration. In one case there were large amounts of bloody frothy sputum for many months, in another the patient noted a sweetish taste to the sputum, while in another case the sputum had a distinct yeast-like odor. In only two cases was there frank hemoptysis. In four cases there was no loss of weight, in three the loss of weight was moderate and in only two cases was it marked. Fatiguability was not an outstanding symptom. In general, pain was a rather prominent symptom. Shortness of breath was present in all cases except two. In the others it was a prominent symptom. Night sweats were present in about half of the cases. Weakness was rather an outstanding symptom, being prominent in seven cases.

The lesion was confined to the lower lobes in seven cases, in one of these the lesion was in the left lower lobe. In the remaining six it was located in the right lower lobes. In only one case was the lesion confined to the apices. In two cases the entire lung was affected, in one of these the process was bilateral.

Geographically the patients came from all sections of the United States. In general, the symptomatology is that of any chronic pulmonary infection. Although certain symptoms such as paroxysmal cough, chest pain and shortness of breath are prominent they are not sufficiently characteristic to be of much value in establishing a diagnosis. The fact that these are predominatingly basal lesions would in itself suggest that they are non-tuberculous.

Blood Picture Contrary to some reports, marked changes in the blood picture were not present, there being eosinophilia in only one case and

TABLE III
Clinical Findings

Case	Locality	First Consult	Age	Sex	Symptoms Began	Initial Symptoms	Cough	Expectoration	Hemoptysis	Lost Weight	Tiredness	Pain	Short Breath	Night Sweats	Weakness	Lesion in	Outcome
1	W Va	Jan 1924	52	F	4½ yrs ago in W Va	Acute influenza	Very severe	Considerable	Continuous	None	Marked	Moderate	On exertion	None	Marked	Rt middle lobe	Died Jan 1925
2	Va	Jan 1925	21	M	4 yrs ago U S Navy	Pleurisy and bronchitis	Severe	Considerable	Sputum tinged	None	Moderate	Constant	On exertion	Slight	Marked	Rt lower lobe	Unknown
3	Mo	June 1925	31	M	6½ yrs ago U S Army	Pleurisy and effusion	Severe	Considerable	Sputum tinged	Marked	No complaint	In spine	Considerable	Moderate	Moderate	All lobes	Complete recovery
4	Mich	Sept 1925	24	M	7 yrs ago in France	Acute influenza	Severe	Considerable	Severe	None	No complaint	None	Considerable	None	No complaint	Rt lower lobe	Improved and lost sight of
5	Calif	Nov 1925	30	F	1 yr ago in Calif	Acute influenza	Severe	Slight amount	None	None	Considerable	None	On exertion	None	Slight	Rt middle lobe	Improved and lost sight of
6	Ore	Nov 1926	31	F	6 mos ago in Oregon	Hemoptysis	Slight	Slight amount	Small	Moderate	No complaint	Slight	No complaint	Moderate	Considerable	Rt lower lobe	Improved and lost sight of
7	Calif	Nov 1926	26	F	4 mos ago in Calif	Acute influenza	Very severe	Slight amount	None	Moderate	Considerable	Moderate	Noticeable	Moderate	Considerable	Left lower lobe	Complete recovery
8	Ill	June 1933	47	M	2 yrs ago in Illinois	Pleurisy	Very slight	Very slight amount	None	Marked	Marked	Severe	Very marked	None	Very marked	Both pleurae Both upper lobes	Died July 1933
9	Ariz	July 1933	58	M	4 mos ago in Ariz	Acute influenza	Considerable	Considerable	None	Moderate	No complaint	Severe	None	None	Considerable	Rt lung all lobes	Complete recovery

moderate secondary anemia in two cases. Definite leukocytosis was present in two cases. The Wassermann reaction was negative in all nine cases.

Physical Signs The physical signs were rather indefinite. In the seven basal lesions the percussion note was dull with diminished breath sounds and an absence of definite râles in many cases. The apical lesions showed a greater tendency toward bronchial breathing and increased breath sounds, and definite fine crepitations were a more constant finding than at the base.

Roentgen-Ray Findings We found no characteristic roentgenological picture. Suggestive findings were that the lesions were confined largely to the base, that the right lung was more affected than the left and that in all but two cases the apices remained clear. The shadows varied from a few rather dense infiltrative strands extending into the periphery of the lung, to homogenous densities occupying the greater part of the lung field. In some cases there were diffuse strands of stringy woolly density which were unlike any other basal lesion which we have seen and may prove to be of value in differentiating this from other basal lesions.

PROGNOSIS

Of the cases which responded promptly to treatment four may be classified as mild, one as intermediate and one as advanced. Of the two cases which showed no improvement whatever under treatment both were far advanced. The remaining case was lost sight of immediately after the examination was completed and before treatment was instituted.

TREATMENT

All the patients were put on quite intensive bed rest. All were given potassium iodide in increasing doses. Most of these patients could tolerate as much as 75 grains daily but beyond this point gastrointestinal symptoms usually developed. We did not find it necessary to resort to the intravenous or intramuscular use of iodine preparations.

Following the practice of Ashford in the treatment of intestinal moniliasis (sprue) and based on our observation that *Monilia Pmoyi* does not ferment lactose, all commercial sugars were eliminated from the diet in case 9 and milk sugar was substituted. This patient made a spectacular recovery, but since potassium iodide was also given it is difficult to determine what, if any, effect was exerted by the lactose.

CASE VIII

Dr G W, aged 47, was referred to us in June 1933 with a diagnosis of pulmonary tuberculosis. Both the past history and the family history were essentially negative. In August 1931 he developed a pain over the anterior left chest while playing golf. At one of the larger clinics in this country a diagnosis was made of probable malignant growth in the right lower lobe. He continued to work until

TABLE IV
Blood Pictures

Case	Hemo- globin	Red Blood Cells	White Blood Cells	Polynu- clears	Eosin- ophiles	Baso- philes	Small Lymph- ocytes	Large Lymph- ocytes	Total Lymph- ocytes	Large Mono- nuclears	Transi- tionals	Total Mono- cytes	Wasser- mann	Urine
1	75	5080000	10950	35.5	6.5	1	4.5	49.5	54	2	1	3	Negative	Negative
2	100	5220000	8000	49.0	2.0	0	16.0	32.0	48	0	1	1	Negative	Negative
3	88	4800000	15200	78.0	2.0	0	0.0	18.0	18	0	2	2	Negative	Negative
4	83	4844000	6600	56.0	0.0	0	0.0	0.0	43	0	1	1	Negative	Negative
5	95	4744000	12400	74.0	0.0	0	15.0	8.0	23	0	3	3	Negative	Negative
6	80	3824000	10000	61.0	0.0	0	37.0	2.0	39	0	0	0	Negative	Negative
7	90	4272000	10000	75.0	2.0	2	11.0	8.0	19	0	2	2	Negative	Negative
8	67	3280000	5450	54.0	4.0	0	31.5	2.5	34	7.5	5	8	Negative	Negative
9	84	4720000	8750	53.5	2.0	1	37.5	3.5	41	2	5	2.5	Negative	Negative

the spring of 1932 when he visited a number of the larger clinics of Europe. There the consensus seemed to favor a diagnosis of malignancy.

He returned to work in the fall of 1932 at which time he began to run a fever and to feel badly for the first time. In November he became very ill and entered a Chicago hospital where fluid was twice removed from the right pleural space. For the first time a definite diagnosis of malignancy of the right lung was made and a hopeless prognosis given. Following the removal of fluid the patient improved rapidly and gained 20 pounds in weight. In March 1933 he came to Arizona. Shortly after his arrival he again became acutely ill and it was discovered that he had an effusion in the left pleural space. The fluid was removed on two occasions and air substituted. During this time there was no cough or expectoration although the patient complained of chest pain and was intensely dyspneic. On one occasion the patient raised a small amount of sputum which was reported to have contained tubercle bacilli. (In view of the subsequent developments this was probably a technical error.)

When he first came under our observation he was weak and emaciated. The most outstanding symptom was intense dyspnea. He had little cough, occasionally raised sputum, but complained of no chest pain. Perhaps the most striking feature of the case was that during the time he was under our observation the temperature was never above normal. There were many coarse râles over the right lower lobe with marked dullness over the left lower lobe. A few days later the patient expectorated a small amount of sputum which was negative for tubercle bacilli but contained a number of monilia which subsequently proved pathogenic for laboratory animals. Examination of fluid removed from the left pleural space showed monilia which also proved pathogenic on animal injection. Potassium iodide was given in large doses with no favorable effect. The patient grew steadily worse and died on August 24, 1933. A few days before death he developed violent noisy delirium which could be controlled only by large doses of narcotics.

AUTOPSY

Autopsy findings, two hours after death. The body was that of a moderately emaciated white male. External examination of body showed no marks except an old healed scar in the right lower quadrant. The muscles were small and atrophic.

The scalp, periosteum and skull cap were negative. On removing the skull cap there was apparently an increase in the cerebrospinal fluid. The longitudinal sinus and the meningeal vessels appeared engorged with blood. The surface of the brain appeared markedly congested, all fissures between the convolutions and the sub-pial space being filled with a bloody exudate. In the most marked areas there appeared many small white masses. On section of the brain all vessels appeared congested and there was an increase of fluid in the lateral sinuses. The choroid plexus appeared matted together.

Heart The pericardium was negative except for adhesions to both lungs. There was a moderate amount of fat over the surface of the heart. The muscles were relatively firm. On section there was no gross change. The middle cusp of the mitral valve was thickened. The coronary vessels were negative.

Right Lung The pleura was markedly thickened and was adherent at intervals over the entire lung surface producing a series of pockets which, however, contained no fluid. The upper half of the upper lobe showed an area suggesting beginning consolidation but soft in consistency and hyperemic.

Left Lung The pleura was thickened to the same extent as on the right. The lung was about one-half collapsed and the pleural cavity contained 1000 c.c. of fluid. A wide band of adhesions extended along the third rib from the sternum to the axilla. The upper part of the left upper lobe presented the same appearance as that of the

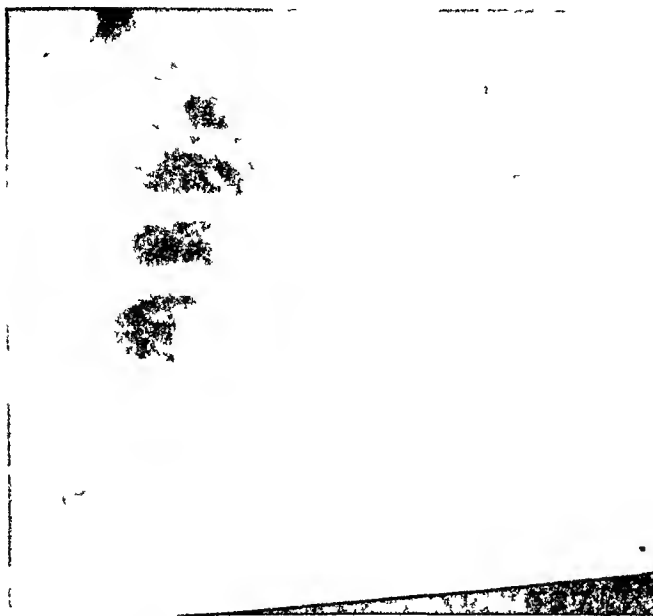


FIG 2 Case 9 (April 7, 1933) Suggestive "stringy woolly" shadows throughout the lower right lung field



FIG 3 Case 9 (July 1, 1933) Kidney-shaped homogeneous shadows covering entire left lung field



FIG 4 Case 9 (August 31, 1933) Following the use of potassium iodide Clearing of the right lung with persistence of the "stringy woolly" shadows especially at the right base

right The lower lobe presented no gross changes The bronchi were dilated to a slight extent and presented the appearance of mild bronchiectasis The bronchial glands were not enlarged and showed no pathologic change The pulmonary vessels of the upper lobes were congested Liver and spleen showed passive hyperemia The other organs were essentially normal

Postmortem Bacteriological Report Cultures were made at autopsy from the small white areas on the brain surface, from the choroid plexus, from the left pleural space and from the pneumonic areas in both upper lobes Without exception all cultures yielded a growth of *Monilia Pinoyi* which upon injection into the pulmonary tissue of rabbits produced characteristic granulomatous nodules Cultures from these nodules yielded *Monilia Pinoyi*

CONCLUSIONS

Bronchomoniliasis is probably a widespread disease and occurs in all sections of this country as well as in the tropics

Many cases go unrecognized, simulating as they do pulmonary tuberculosis in its various clinical forms Early diagnosis is exceedingly important In its early stages the disease responds beautifully to treatment, but in its advanced stages the prognosis is usually hopeless

The final diagnosis is entirely dependent on laboratory findings including animal inoculation If this disease is to be generally recognized it is quite necessary that repeated examinations including cultural studies be made on all questionable sputum

BIBLIOGRAPHY

- 1 CASTELLANI, A Fungi and fungous diseases, Arch Dermat and Syph, 1927, xxi, 383, 571, 714, 1928, xxii, 61, 194, 354
- 2 STOVALL, W D, and PESSIN, S B Classification and pathogenicity of certain monilias, Am Jr Clin Path, 1933, iii, 347-365
- 3 SHAW, F W Monilia from respiratory tract, Jt Lab and Clin Med, 1927, xii, 968-972
- 4 LEWIS, S J Moniliasis of lungs and stomach, Am Jr Clin Path, 1933, iii, 367-374
- 5 HENRICI, A T Molds, yeasts and actinomycetes, 1930, John Wiley and Sons, Inc, New York
- 6 JACOBSON, H P Fungus diseases, 1932, Charles C Thomas, Baltimore
- 7 HOFFSTADT, R E, and LINGENFELTER Pulmonary infection caused by Monilia balcanica (Castellani), Am Jr Trop Med, 1929, ix, 461-467
- 8 BOGGS, J R, and PINCOFFS, M C A case of pulmonary moniliasis in the United States, Johns Hopkins Hosp Bull, 1915, xxi, 407-410
- 9 KOTKIS, A J, WACHAWIAR, M, and FLEISHNER, M S Relation of monilia to infections of upper air passages, Arch Int Med, 1926, xxxvi, 217-221
- 10 HAYTHORN, S R, ROBINSON, G H, and JOHNSON, L Report of a case of early Hodgkin's disease secondarily infected with strain of pathogenic Monilia, ANN INT MED, 1932, vi, 72-81
- 11 SMITH, L W Role of monilia psilosis (ashfordi) in experimental sprue, Jr Am Med Assoc, 1924, lxxviii, 1544-1549
- 12 GALBRFATH, W R, and WRISS, C Bronchomoniliasis, Arch Int Med, 1928, xlii, 500-507
- 13 STOVALL, W D, and GRFLIFY, II P Bronchomycosis, Jr Am Med Assoc, 1928, xci, 1346-1351
- 14 GROSSI, G, and BALOG, P Clinical and experimental studies in Castellani's pulmonary moniliasis, Jr Trop Med, 1929, xxxii, 253-262
- 15 WARR, O W Bronchomoniliasis, clinical and pathological study, with report of illustrative cases, ANN INT MED, 1931, v, 307-332

THE TREATMENT OF ACUTE MERCURIC CHLORIDE POISONING ¹

By EDGAR HULL, M D , and LOUIS A. MONTE, M D ,
New Orleans, Louisiana

IN 1915 Lambert and Patterson ¹ proposed a method of treatment for bichloride poisoning, designed primarily to accelerate the excretion of mercury from the body. Since that time the gradual acquisition of knowledge concerning this intoxication has led to innovations in its therapy. Various workers have from time to time advocated procedures designed to prevent certain of the toxic effects of mercury, and to combat certain of the physiologic disturbances occasioned by its presence in the body.

Naturally, a large part of the investigations in the therapy of mercury poisoning has centered about the search for chemical antidotes, which would prevent the absorption of mercury or render innocuous that which has been absorbed. Among the substances recommended have been calcium sulphide,² sodium phosphite,³ sodium hypophosphite and hydrogen peroxide,⁴ acacia,⁵ hydrogen sulphide⁶ and sodium thiosulphate.⁷ While it is likely that some of these substances prevent the absorption of mercury to a certain extent, it is decidedly improbable that any of them mitigates the toxic effect of absorbed mercury.

The method of treatment proposed by Lambert and Patterson ¹ was based on the premise that the chances of recovery might be enhanced by the rapid elimination of mercury from the body. Large volumes of fluid were given by mouth and by rectum in order to sweep mercury out through the kidneys, the stomach and colon were washed out frequently to remove mercury excreted into them. Alkaline salts were given by mouth and by proctoclysis, possibly to combat the acidosis of mercury poisoning, but more likely because of their diuretic effect.

The first treatment frankly aimed at rectification of disturbed physiology was introduced by Weiss,⁸ who administered alkali by mouth and by vein to combat the acid intoxication [described by MacNider⁹] and who advocated the use of hypertonic salts to reduce "colloidal swelling of the tissues."¹⁰

In 1916 Lewis and Rivers¹¹ and in 1917 Campbell¹² reported marked reduction of plasma chloride in severe mercurial intoxication. Hayman and Priestley,¹³ Peters and Van Slyke¹⁴ and Lemierre, Laudat and Laporte¹⁵ advocated parenteral administration of saline to compensate for the chloride deficit.

Haskell, Carder, and Coffindaffer¹⁶ in 1923 demonstrated the value of forcing fluid parenterally in experimental mercury poisoning. In several

* Received for publication April 17, 1935

From the Departments of Medicine, Louisiana State University School of Medicine and the State Charity Hospital, New Orleans, La.

methods of treatment, fluid was forced,^{1, 8, 17} but little stress was laid on the employment of parenteral routes of administration

Shock, the cause of death in almost a fourth of the patients who die from the ingestion of mercuric chloride,¹⁸ was apparently ignored in the older methods of therapy. The first mention, so far as we know, of measures to combat shock in mercury poisoning, was made very recently by Peters, Eisenman and Kydd,¹⁹ who propose a method of treatment, the aim of which is the "prevention or rectification of the functional disturbances caused by mercury"

An analysis of the case records of all patients treated for acute mercury poisoning at Charity Hospital during the last 16 years [302 cases in all¹⁸] showed that no progress in therapy had been made during this period. Throughout these years, with varying methods of treatment, the mortality remained about 25 per cent. About half of the patients reputed to have taken mercuric chloride developed signs of mercury poisoning, and about half of these died. During the early part of this period, 1917 to 1924, either the Lambert and Patterson method or the Weiss treatment or a combination of the two was used. From 1924 to 1930, the treatment remained unchanged, except that sodium thiosulphate was given to nearly all patients. After 1930, most of the patients were given infusions of 10 per cent glucose daily, and occasionally infusions of normal salt solution, in addition to the other treatment. The mortality was almost exactly the same in cases which were given sodium thiosulphate as in those which did not receive it.

In July 1932, we instituted certain changes in therapy, which seemed logical to us, considering the anatomic lesions and the disturbed physiology of mercury intoxication. The modified form of therapy employs chiefly certain principles of other methods and cannot, therefore, be considered a new treatment. It is, in fact, identical in most details with the form of therapy proposed by Peters, Eisenman, and Kydd,¹⁹ whose work antedates ours. This paper is concerned with the results obtained by this method of treatment in 34 patients who had ingested bichloride of mercury.

METHOD OF TREATMENT

1 *The Usual Emergency Measures* Milk is administered, followed by gastric lavage*. A saline cathartic is introduced into the stomach before the tube is withdrawn provided no shock is evident.

2 *Introduction into the Body of an Adequate Amount of Fluid* For the first 48 hours the amount given is arbitrarily set at 4000 to 6000 cc daily. This is thought to be sufficient to prevent dehydration which might otherwise result from vomiting and diarrhea. Later the fluid intake is gauged by the approximate amount of water lost in vomiting and diarrhea, and by the output of urine. Most of the fluid is given intravenously or

* No antidote was given to the 34 patients, all of whom were treated prior to the publication of Rosenthal's²⁰ work on the use of sodium formaldehyde sulfoxylate. Our experiences with this antidote have been reported elsewhere.²¹

subcutaneously early in the intoxication, even though there is little or no vomiting, because of the frequent occurrence of gangrenous lesions of the stomach and upper bowel in these patients¹⁸ The most convenient method of supplying fluid is the employment of a slow intravenous drip

3 *The Use of Salt and Glucose* These are given to prevent hypochloremia and acidosis, and to mitigate protein destruction They are usually employed together, equal parts of 10 per cent glucose and normal saline being used in the intravenous drip

4 *The Administration of Alkalis* If the patient is not vomiting, he is given four grams of sodium citrate every three or four hours If he desires fluid, he may take small amounts of imperial drink, well-sweetened fruit drinks, or water

This regime is varied according to the exigencies of each case If toxic manifestations appear, therapy is regulated according to the symptoms and their severity The important symptoms in severe intoxications are shock, vomiting, abdominal distention, diarrhea, oliguria and anuria, and stomatitis Vitiated physiologic processes are indicated by elevation of the non-protein nitrogen of the blood, by decrease of blood chloride, and diminution of plasma bicarbonate

Shock An initial hypodermic dose of morphine is given to allay pain, which is probably partly responsible for shock An infusion of glucose in salt solution is begun, caffeine sodium benzoate is given intravenously and adrenalin intramuscularly After the institution of these measures, the stomach is washed out We consider it important that lavage be delayed until measures have been taken to combat shock, since attempts at immediate lavage may aggravate the collapse already present, the patient may even die during the attempted lavage procedure

If shock is not relieved by these measures, a transfusion (500 c c of citrated blood) is given as soon as possible, 0.3 c c of adrenalin is injected intramuscularly every 20 to 30 minutes, and 0.5 gram of caffeine sodium benzoate is given intravenously every three hours

Vomiting, Distention, Diarrhea Continued vomiting usually co-exists with tympanites Nothing at all is given by mouth, the stomach is washed out gently with normal saline, the tube left in and aspirated at intervals Extra fluid and salt are supplied intravenously to replace that removed by aspiration A rectal tube is inserted and a heat tent placed over the abdomen For protracted distention hypertonic salt solution is given intravenously, as recommended by Ochsner and Gage²² in the therapy of adynamic ileus (5 c c of distilled water and 20 c c of concentrated Hartmann's solution)

Diarrhea is seldom as troublesome as vomiting, usually subsiding spontaneously after a few days We use colonic irrigations of warm normal saline and give opium and bismuth subnitrate by mouth if diarrhea persists

Oliguria and Anuria It is difficult to state how much water and salt it is advisable to give a patient who is secreting no urine or very small amounts

It is possible that mechanical blockage of the renal tubules by necrotic, swollen epithelium may be concerned in the mechanism of anuria in mercury poisoning²³, a large intake of fluid, which favors increased glomerular filtration, might tend to "force the renal block"²⁴. The work of Bariy, Shafston and Ivy²⁵ on nephrectomized dogs also indicates that the parenteral administration of fluid and salt might prolong the lives of anuric patients until such a time as secretion of urine will be reestablished. It is, however, dangerous to give large amounts of water and salt to patients with anuria. Although edema is not usually a part of the clinical picture of bichloride poisoning,²⁶ it can be constantly produced if large amounts of water, together with salt, are given to these patients²⁷. While moderate subcutaneous edema may not be harmful, the continued forcing of fluid and salt may result in rapidly developing massive pleural, pericardial and peritoneal effusions, and the patient may die suddenly of acute heart failure. We have seen this happen to two patients, one of whom was under the care of one of us (E. H.). At present we feel that in the absence of edema, it is safe to give 3000 cc of water daily, above the amount lost via the gastrointestinal tract, approximately the amount required by a normal individual (including the water derived from food),²⁸ and to push the administration of salt as long as the blood chloride is below normal. When any edema at all appears, it seems advisable to reduce the fluid intake, and to give very little saline, if any at all, it is probably unsafe to give more than 1500 to 2000 cc of fluid in excess of that lost in stools and vomitus. [Approximately 1800 cc of water are lost each day via the skin and lungs in a normal person²⁹].

Diuretics have been used in all patients with anuria or severe oliguria. Fifty cc of 50 per cent glucose are given intravenously twice a day, and 0.5 gram of theophylline ethylene diamine* intravenously daily for three or four days. On occasion, we have tried potassium chloride by mouth (6 to 8 grams daily) and intravenously (300 cc of 1 per cent solution). While no apparent deleterious effects have followed the use of any of these substances, we have not observed striking diuresis following the administration of any of them.

Hypochloremia If the blood chloride remains below normal, in spite of the administration of normal saline, 2 per cent sodium chloride solution is substituted. Marked reduction of blood chloride was not encountered in any patients reported in this series.

Acidosis The carbon dioxide combining power of the blood plasma is determined daily on all severely toxic patients. When, on the usual therapeutic regime, this falls below 40 volumes per cent, alkalis or buffer salts are given intravenously. We have used Hartmann's solution, molar sodium lactate (Hartmann), Fischer's solution, and sodium bicarbonate (2.5 to 5 per cent solution). At present we are using sodium bicarbonate in 5 per cent solution, when the indication for intravenous alkali therapy is present†. All

* There is evidence that this drug produces diuresis by increasing glomerular filtration.³⁰

† Experience with the intravenous use of sodium bicarbonate in acidosis indicates that 500 cc of 5 per cent solution usually increase the CO₂ combining power about eight volumes per cent.

of these preparations, because of their sodium content, may aggravate pre-existing edema, and should be used very cautiously in its presence. We believe that the presence of edema contraindicates the use of Fischer's solution, in one patient, a marked increase of edema, with hydrothorax and ascites, followed its use.

Other Symptoms Mouth washes containing sodium perborate or potassium permanganate are used for stomatitis. Morphine and phenobarbital sodium are given freely when sedation is required. Calcium gluconate (1 gram) is given intravenously for muscular twitchings in patients with uremia, the twitchings are probably due to hypocalcemia³⁰. Transfusions are given if much bleeding from stomach or bowel occurs.

RESULTS OF THERAPY

Thirty-four patients reputedly poisoned with mercuric chloride were treated according to this method, there were three deaths, a mortality of approximately 9 per cent. Since in the past, the mortality following bichloride ingestion has been about 25 per cent in Charity Hospital,¹⁸ it might appear at first glance that the newer therapy is strikingly superior to the methods formerly in use. A close analysis of the cases, however, shows that there is no occasion for enthusiasm.

Of the 34 patients, only 10, less than a third, developed any signs at all of mercury poisoning, whereas, in the past, about half of the patients had manifested definite signs attributable to the toxic effects of mercury¹⁸. Since so many variable factors, difficult to ascertain reliably, determine whether toxic symptoms appear at all, and since we see no reason why this method of therapy should prevent the appearance of all the manifestations of mercury poisoning, we must attribute the lower incidence of "toxic" cases in this series, not to any effect of treatment, but to the fact that in a larger proportion of these patients, the amount of mercury absorbed was not sufficient to be poisonous. The lower mortality, therefore, does not necessarily signify improved therapeutic results.

The mortality in the 10 "toxic" cases is 30 per cent, which is lower than that in "toxic" cases treated in the past by other methods (50 per cent),¹⁸ but not significantly so, in view of the small number of cases in the present series. In five of the 10 cases, the intoxication was mild or only moderately severe, and it seems likely that these patients would have recovered without any special therapy, although it is of course possible that the therapy employed mitigated the severity of the intoxication. Any claim for merit of the therapy employed must be based upon results in the five cases in which the intoxication was markedly severe. Had all of these patients, or four of the five, recovered, this would have constituted strong evidence of merit of the treatment, but three of the patients died, one early in shock, two of uremia. It is thus clear that this series offers no statistical evidence

* The mortality of severe mercury poisoning in Charity Hospital has been almost 90 per cent.¹⁸

to prove the superiority of this method of therapy. The recovery of one patient in whom the prognosis, from an appraisal of the early signs, seemed very unfavorable, is the only indication that therapy directed towards the combatting disturbed physiologic processes may occasionally be life-saving in severe mercury poisoning.

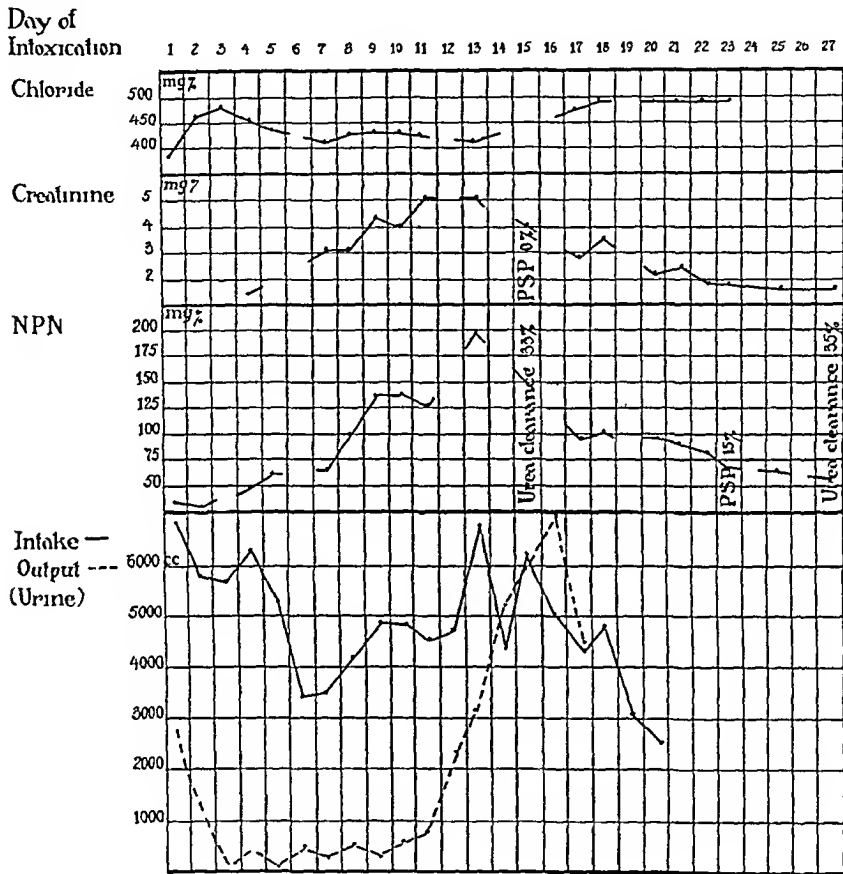


CHART I

CASE I

A white female, aged 23, took 10 bichloride tablets (73 grams) dissolved in a glass of water, she had eaten a sandwich and drunk some beer a short time before ingestion of the poison. Vomiting occurred in less than five minutes, gastric lavage was done a half hour later. Vomiting continued, and bloody diarrhea appeared in about two hours.

After the usual emergency measures, glucose and saline were given continuously by intravenous drip. During the first 24 hours, she received a total of 6800 c c of fluid, of which only 1800 c c were given by mouth. During this period the output of urine was 2800 c c.

Diarrhea lasted only two days, vomiting persisted for a week. Abdominal distention was marked. Stomatitis appeared on the third day. On the sixth day, a necrotizing lesion of the vagina was observed. Marked oliguria developed on the third day and persisted for eight days, the daily output varying from 150 to 500 c c.

The urine passed during this period was of very low specific gravity (1 000 to 1 004), and contained only small amounts of albumin and a few casts (Chart 1)

The non-protein nitrogen of the blood rose gradually, on the tenth day of the intoxication, it had reached 133 mg per cent. No significant diminution of blood chloride occurred. Edema of the face and legs appeared on the fourth day, at this point, part of the chloride intake was given as potassium chloride. What was considered to be adequate amounts of fluid (in reality, perhaps too much) was supplied by vein and hypodermoclysis, and by mouth after vomiting and tympanites had subsided.

Fifty c c of 50 per cent glucose were given intravenously every day during the period of oliguria, twice she received 0.5 gram of metaphyllin intravenously. Edema of the face and extremities increased, and signs of ascites appeared. On the eleventh day, while an intravenous drip was running, she experienced a sudden attack of dyspnea, after an injection of morphine and discontinuance of the drip, the attack subsided promptly.

On the twelfth day, there was a sharp rise in the output of urine, from this day diuresis was maintained, edema diminished, and recovery was rapid. Clinical improvement as evidenced by copious diuresis preceded the fall of the N P N level, on the thirteenth day, when 3200 c c of urine were voided the N P N reached its highest level, 190 mg per cent. On the fifteenth day, when 5000 c c of urine were passed there was no phthalein excretion after two hours, and the N P N was 150 mg per cent.

The patient was discharged 34 days after ingestion of the poison, apparently in good health.

Most of the factors that determine the prognosis in mercury poisoning indicated an unfavorable outlook for this patient, in spite of the early vomiting and the fact that her stomach was not empty. The dose was more than sufficient to kill, the drug was taken in solution, and severe toxic manifestations appeared early.¹⁸ The long duration of oliguria and the high levels that the non-protein nitrogen and creatinine reached also bespoke a poor prognosis.¹⁸ It may be significant that the non-protein nitrogen of the blood rose very slowly in the presence of such marked diminution of urinary output, and that there were no uremic manifestations.

SUMMARY

1 Thirty-four patients, who ingested bichloride of mercury, have been treated by a method designed chiefly to prevent and combat the physiologic disturbances occasioned by the presence of mercury in the body. The method is almost identical with the one proposed recently by Peters, Eisenman, and Kydd.

2 Only 10 of the patients developed any signs of mercury poisoning. In five, the intoxication was mild or of moderate severity, in the remaining five it was very severe.

3 Three patients died, a mortality of approximately 9 per cent. Although in the past, the mortality of mercury poisoning in Charity Hospital has been about 25 per cent, a study of the individual cases in the present series indicates that the lower mortality is not necessarily due to the changed method of therapy.

REFERENCES

- 1 LAMBERT, S W, and PATTERSON, H S Poisoning by mercuric chloride and its treatment, *Arch Int Med*, 1915, *vi*, 865-879
- 2 WILMS, J H Calcium sulphide as the chemical and clinical antidote for mercuric chloride poisoning, *Jr Lab and Clin Med*, 1917, *ii*, 445-458
- 3 CARTER, T A Mercuric chloride poisoning, *Chicago Med Rec*, 1914, *xxvi*, 444-460
- 4 FANTUS, B, and HYATT, E G Antidotes in mercuric chloride poisoning, *Jr Lab and Clin Med*, 1917, *ii*, 813-818
- 5 ZEIGLER, W H A study of the efficacy of certain antidotes in the treatment of acute bichloride of mercury poisoning, *Jr Lab and Clin Med*, 1925, *vi*, 259-268
- 6 SABBATANI, L *Biochem Centralbl*, 1906, 502 (Quoted by Wilms²)
- 7 DENNIE, C C, and MCBRIDE, W L Treatment of arsenic dermatitis and certain other metallic poisonings, *Arch Dermat and Syph*, 1923, *vii*, 63-76
- 8 WEISS, H B Methods of treatment of mercuric chloride poisoning, *Jr Am Med Assoc* 1917, *lxviii*, 1618-1620 Mercuric chloride poisoning, *Arch Int Med*, 1924, *xxviii*, 224-229
- 9 MACNIDER, W DFB Study of acute mercuric intoxication in dog, *Jr Exper Med*, 1918, *xxvii*, 519-538
- 10 FISCHER, M Edema and nephritis, 1921, 3rd Ed, John Wiley and Sons, New York, p 735
- 11 LEWIS, D S, and RIVERS, T M Chemical studies on a case of bichloride poisoning, *Johns Hopkins Hosp Bull*, 1916, *xxvii*, 193-201
- 12 CAMPBELL, W R Acute mercuric chloride nephrosis, *Arch Int Med*, 1917 *xx*, 919-930
- 13 HAYMAN, J M, JR, and PRIESTLEY, J T Importance of diuresis in treatment of certain cases of mercuric chloride poisoning, *Am Jr Med Sci*, 1928, *clxxvi*, 510-516
- 14 PETERS, J P, and VAN SLIKE, D D Quantitative clinical chemistry, Vol 1, 1931, Williams and Wilkins, Baltimore, p 1156
- 15 LEMIERRE, A, LAUDAT, M, and LAPORTE, A Deux cas de nephrite mercurielle traites par la choruration, *Presse med*, 1932, *xl*, 1637-1640
- 16 HASKELL, C C, CARDER, J R, and CORINDAUFER, R S Value of forcing fluid in treatment of mercuric chloride poisoning, *Jr Am Med Assoc*, 1923, *lxxxi*, 448-450
- 17 ROSENBLUM, J Studies in a case of acute bichloride of mercury poisoning, *Am Jr Med Sci*, 1919, *clvii*, 348-356
- 18 HULL, E, and MONTE, L A Bichloride of mercury poisoning, a statistical study of 302 cases, *South Med Jr*, 1934, *xxvii*, 918-924
- 19 PETERS, J P, EISENMAN, A J, and KYDD, D M Mercury poisoning, *Am Jr Med Sci*, 1933, *clxxxv*, 149-171
- 20 ROSENTHAL, S M Antidote for acute mercury poisoning, *Jr Am Med Assoc*, 1934, *cii*, 1273-1276
- 21 MONTE, L A, and HULL, E Bichloride of mercury poisoning, sodium formaldehyde sulphonylate as antidote, *South Med Jr*, 1934, *xxvii*, 988-990
- 22 OCHSNER, A E, and GAGE, I M Adynamic ileus, *Am Jr Surg*, 1933, *xx*, 378-404
- 23 FISHBERG, A M Hypertension and nephritis, 1931, Lea and Febiger, Philadelphia, p 280
- 24 VOLHARD, F Mohr and Stachelin's *Handbuch der inneren Medizin*, 1918, *iii*, 1554, J Springer, Berlin
- 25 BARRY, F S, SHAFTON, A L, and IVY, A C Experimental edema in nephrectomized dogs, role of water and chlorides, *Arch Int Med*, 1933, *li*, 200-206
- 26 FISHBERG, A M See reference 23, p 282
- 27 HULL, E, and MONTE, L A Unpublished studies
- 28 HOWELL, W H Text-book of physiology, 12th Ed, 1933, W B Saunders, Philadelphia, p 911
- 29 HERRMANN, G, STONE, C T, SCHWAB, E H, and BONDURANT, W W Diuresis in patients with congestive heart failure, *Jr Am Med Assoc*, 1932, *xcix*, 1647-1652
- 30 FISHBERG, A M See reference 23, p 137

"EVENTRATION" OF THE RIGHT DIAPHRAGM REPORT OF A CASE WITH REVIEW OF THE LITERATURE, CHIEFLY FROM THE STANDPOINT OF ETIOLOGY AND DIAGNOSIS *

By L. FELDMAN, M D , I. M. TRACE, M D , F A C P , and M. I. KAPLAN, M D , *Chicago, Illinois*

THE condition commonly called "eventration" of the diaphragm is understood to mean an abnormally high position of one-half of the phrenic leaf, caused not simply by displacement, but by aplasia (congenital), or atrophy (acquired) of the muscle fibers of the half of the diaphragm. As a result, the abdominal viscera are displaced upward into the thoracic cavity. The unduly expanded leaflet is intact and its position is permanent.

This abnormality has passed into the literature under more names than any other lesion of the diaphragm. The names, "elevation," "relaxation," "high position," "insufficiency" and "dilatation" have been used to designate this pathological state. While eventration is a gross misnomer, since it suggests the displacement of the viscera out of the abdomen, it has received by custom a connotation which is specific for this condition of the diaphragm (Bayne-Jones).

A brief review of the development of the diaphragm¹ is warranted in order better to understand this abnormality. The anterior end of the celom containing the heart is shut off by a partition which forms at about the sixth week of intrauterine life, and at a slightly later date, the two pleural sacs are separated from the peritoneal cavity by the completion of the diaphragm. The greater part of the latter is formed from the septum transversum, which is ventral in situation, while the dorsolateral portions are derived from the pleuroperitoneal membranes which close the communicating ducts between the two cavities on the right and left sides.

The musculature of the diaphragm is stated to be developed from two muscle masses derived from the fourth cervical myotome¹. These grow into the developing diaphragm, while the septum transversum is still in the cervical region. Later the diaphragm migrates caudally to reach the proper place.

In eventration the cupola forms a thin sac with normal attachments, but projecting into the thorax to reach a high level. It seems probable, therefore, that neither failure of migration nor a failure in the union of the component parts is responsible for the condition, but that it is due to failure of development of the musculature on one side. As a result of this, the muscle sheet is almost entirely replaced by a thin membrane, which yields very readily to abdominal pressure¹.

* Received for publication March 15, 1935

From the Departments of Medicine and Roentgenology, Mount Sinai Hospital, Chicago, Illinois

However, there have been varied opinions as to the etiology of eventration ever since its discovery (1784) Thoma² believed that the condition was secondary to congenital malformation of the lung on the affected side, and that the diaphragm rose to fill the space in the pleural cavity Doering,³ on the other hand, favored the view of a primary deficiency of half of the diaphragm The symmetrical condition of the thorax in eventration he employed as an argument in favor of his view Clinical experience in chronic diseases of the chest associated with elevation of the diaphragm due to traction from adhesions demonstrates that malformation and asymmetry of the chest wall are usually the result Falkenstein⁴ has shown that idiopathic degeneration of the diaphragm frequently occurs, the lesion being a fatty degeneration of the muscle Aronson⁵ enumerates many diseases that may affect the motor columns of the cervical cord, and thus give rise to an acquired eventration He also lists neuritis of the phrenic nerve as a possible cause Christian⁶ strongly believes that the cause of eventration is congenital That it is frequently seen in infants, that there is no history of trauma, and that the affected lung is not compressed, are arguments he employs in favor of his view

At autopsy the lung on the affected side is usually small and hypoplastic, but atelectasis has not been observed The eventrated diaphragm is a thin translucent membrane, containing a few muscle fibers and smoothly covered by pleura and peritoneum The phrenic nerve is usually reduced in size, but otherwise normal

The first authentic case of eventration is that of Petit⁷ in 1790 He himself did not employ the term "eventration" but considered the condition a peculiar variety of diaphragmatic hernia Cruveilhier⁸ in 1849 was the one to coin the name eventration and elucidate the essential differences between hernia and eventration Bamberger⁹ in 1913 compiled 31 cases Bayne-Jones¹⁰ in 1916 collected 41 cases Glaser¹¹ in 1901 was the first to diagnose this condition during life Hirsch¹² in 1901 was the first to make a roentgenological diagnosis He diagnosed hernia of the diaphragm and eventration was found at autopsy There were over 100 cases of eventration reported in the literature up to 1926 The greater number of instances of this rare anomaly occur on the left side Korns¹³ in 1921 critically reviewed the literature and found only 18 proved cases of left eventration and 41 which, though not proved, seemed reasonably certain, thus making a total of 59 cases The same author listed only the following five cases of eventration of the right diaphragm Two of Eppinger's in 1911 which were substantiated by necropsy, a case by Glassner in 1916, a fourth case, described in 1916 by Bayne-Jones, who made the diagnosis purely by physical examination, subsequent roentgenological examination and laparotomy confirming his clinical impression, and Aronson's case reported in 1918, which Korns considers not completely proved because of the author's vague description of the findings If genuine, it is the fifth case Korns' own case makes a sixth He diagnosed his case by roentgen-ray and physi-

cal findings, based on the physiology of the intercostal muscles and the diaphragm. He concluded that of these six cases, in four the diagnosis may be considered proved, while in two it is not proved but reasonably certain.

Golob¹⁴ in 1926 reported a case of right eventration, proved at operation. Fatou and Prevost¹⁵ described a case of right eventration in 1928, thus raising the number of cases to eight. Morris'¹⁶ case in 1929 of right sided eventration with transposition of the stomach, colon and liver, diagnosed by the roentgen-ray is the ninth. Our case of right eventration is the tenth to be described.

Eventration of the diaphragm should not be looked upon as just a rare curiosity to be relegated to the pathological museum. Recognition of this abnormality is important in order to prevent confusion with other conditions situated above and below the diaphragm. Without the assistance of the roentgen-ray, eventration has been mistaken for pleural effusion, encysted empyema, and abscess of the lung. Exploratory thoracenteses have been performed. The results of this procedure may be very tragic. The discovery of eventration in women of the child-bearing age is very important for it may turn out to be a menace to life. In one instance¹⁷ where a complication precipitated labor before a planned Caesarean section was undertaken, the patient died because of a ruptured diaphragm. In our case forceps had to be applied in the second stage of labor, because her "bearing down" was of no avail. At that time, however, it was not known that she had such an anomaly of the diaphragm.

This anomaly is also important because of the readiness with which it may be confused with diaphragmatic hernia. The latter condition often lends itself to surgical repair, but in eventration operation is useless. The differentiation, however, between these two conditions may be impossible even after resorting to all available safe methods of investigation, short of an exploratory laparotomy.

There are no distinctive symptoms of eventration of the diaphragm. In most instances it is asymptomatic, since both the thoracic and abdominal viscera accommodate themselves to this congenital defect. However, there may be some cardiac, pulmonary, or gastric symptoms: palpitation, slight dyspnea, "gas" pains after meals, asthmatic attacks or substernal pain. Cyanosis and weakness have been observed as well as nausea and vomiting.

The condition may be suspected on physical examination, but in most instances it has been discovered as the result of roentgen-ray examination or at autopsy. The usual findings are absence of Litten's shadow, dullness, and absence of breath sounds on the affected side. The chest is symmetrical and the inspiratory expansion of the two sides of the chest, with the exception of the costal margins, is the same. In right sided eventration the position of the heart is not changed to as appreciable a degree as it frequently is in left eventration. Tympanic sounds may be elicited over the affected side of the thorax, depending greatly on how much food or gas

there is in the viscera during the examination Peristaltic sounds in the chest are very significant, but Lord¹⁸ cautions against this finding He states that normally, peristaltic sounds may be heard on the left side as high as the third rib in front and lower third of scapula behind, and at a somewhat lower level on the right side These peristaltic sounds are much louder on the left than on the right

However, there is a physical sign, which, according to Korns¹³ and Lord,¹⁸ is the most valuable and the least used in the diagnosis of eventration of the diaphragm It is the Hoover sign—an exaggerated inspiratory divergence from the median line of the entire costal margin on the affected side It is elicited with the patient in the recumbent position This sign is based on the work of Hoover¹⁹ on the physiology of the diaphragm and of the intercostal muscles

The diaphragm and the intercostal muscles are antagonists The former increases the longitudinal diameter, while the latter increase the transverse and the anteroposterior diameters of the thorax The excursion of the abdominal wall is a measure of the excursion of the diaphragm The lower six intercostal muscles and the diaphragm are also antagonists in controlling the movements of the costal border Unopposed by the phrenic action, the intercostal muscles will cause the entire costal margin to move away from the median line, and unopposed by the intercostals the diaphragm will draw the entire costal margin toward the median line Hence, the movement of the costal margin during normal inspiration is the resultant of the opposed actions of the intercostal muscles and the diaphragm¹⁹

The extent to which the diaphragm is able to oppose the intercostal muscles depends upon the arch, and the more nearly the curve approaches a plane, the greater is its mechanical advantage¹⁸ If the diaphragm is at a mechanical disadvantage by upward displacement, or if its muscles are injured, the pull of the intercostal muscles is more effective The result is a distinct inspiratory widening of the subcostal angle, caused by the exaggerated inspiratory divergence from the median line of the entire costal margin, from the xyphoid to the post-axillary line

Korns¹³ urges the use of palpation besides inspection in eliciting this sign The palpation should be applied to the extreme ends of the ribs of the costal margin, and not to the arcs of the ribs The movement of the latter is upward and outward in a "bucket-handle" fashion in response to normal activation of the intercostal muscles Thus in obese patients palpation, we think, may elicit this outward excursion of the costal margin, while inspection may not Such was our experience with our case

The evidence of activation or want of activation of half of the phrenic leaf is especially of value in the differential diagnosis between hernia and eventration¹³ of the diaphragm In hernia, Hoover's sign is not observed, unless in a very marked herniation with a very extensive aperture, which is exceptional If there should be any asymmetry in movement, it occurs as a lessened outward movement on the affected side, due either to a flattening of

the diaphragm, or to its acquisition of a high insertion from the formation of pleural synechiae between it and the thoracic wall

Eventration of the diaphragm must, naturally, also be differentiated from such conditions as pneumothorax, subphrenic abscess, large basal cavities, and paralysis of the diaphragm

In most instances eventration is discovered as a result of roentgenological study, and such studies constitute the most reliable laboratory procedure we have. Walton²⁰ enumerates the following diagnostic roentgenological signs

(1) *High position* of the affected diaphragm is present, and it may be as high as the second interspace

(2) *Regular* contour of the arched line is a sign stressed very much. There is always present the typical curved line of the dome of the diaphragm. In hernia, the contour of the arch is somewhat irregular and usually nodular,²¹ and when an opaque meal is given, marked derangement of the arch by the new shadow is seen. However, this finding does not absolutely differentiate eventration from a hernia in which the contour of a dilated stomach or colon may give a similar regular arched line

(3) *Excursion* of the affected half of the phrenic leaf is usually present, but very much limited. Under the fluorescent screen, the normal side exhibits normal excursion, and there is no evidence of exaggeration to compensate for the affected side. When the patient is instructed to breathe deeply, the abnormally elevated diaphragm will be seen to move slightly up and down to the extent of probably a few centimeters only

(4) *Paradoxical movement* of the affected side of the diaphragm as a test has no great significance. Assmann²¹ comments on the unreliability of this sign. For a time this was regarded as a distinguishing sign, but recent observers agree that respiratory movement may be normal, diminished, absent, or reversed in either eventration or hernia.²²

(5) *Inspiratory excursion* of the mediastinum toward the sound side has been observed three times according to Korns.¹³ This phenomenon is due to the development of a relatively greater degree of negative pressure in the sound side because of the presence of diaphragmatic contraction on that side. Similar phenomena may be observed in unilateral paralysis of the phrenic nerve. The reverse is usually seen in bronchial obstruction, where the excursion of the mediastinum is toward the affected side. While this sign should be looked for in suspected eventration it is very often absent, and when present, its value in differential diagnosis is questionable.²⁰

(6) *Displacement of the heart* is frequently seen in left sided eventration thus giving rise to dextrocardia. Whenever the latter is diagnosed, the condition of the left diaphragm should be investigated. In right sided eventration the heart is usually not appreciably displaced. It seems that the displacement of the heart in right sided eventration depends upon what organs are prolapsed into the thorax. When the liver is high up, the heart is pushed over to a much lesser degree than when the big bowel is high in

the thorax In our case, a barium enema produced quite a bit of distress, because the distention of the colon displaced the mediastinal structures still more to the left

(7) *Pneumoperitoneum* is classified among the diagnostic signs Walton,²⁰ after enumerating the roentgenological findings discussed above, concludes that the only pathognomonic finding in eventration of the diaphragm is a distinguishable separation of the arched line of the dome of the diaphragm from the viscera below, accomplished by injecting air into the peritoneal cavity Lord¹⁸ questions whether this procedure is justified, since in the presence of a diaphragmatic hernia, pneumoperitoneum may entail some risk The absence of a sac in the majority of cases of diaphragmatic hernia, and the imperfect closure of the defect in the diaphragm by the hernia, make it likely that the introduction of gas into the peritoneal cavity will cause a pneumothorax He also cites the case of Schlect and Wels who used this method in a congenital diaphragmatic hernia Three weeks later their patient developed severe abdominal pain, followed by collapse The operation revealed perforation and gangrene of the greater curvature of the stomach The possibility that the pneumoperitoneum, by displacing the stomach and interfering with its blood supply, might have been responsible, could not be excluded by them Lord¹⁸ feels that if the symptoms are severe and more suggestive of a hernia than of eventration, it is better to do an exploratory operation and repair the hernia if found and feasible, than to subject the patient to the risk of a pneumoperitoneum This procedure was not employed in our case

(8) Lateral roentgen views of the chest are of diagnostic help in abnormalities of the diaphragm Their employment is often mentioned in the British literature^{1,16} as a means of differentiating eventration from hernia of the diaphragm In the former, the lateral view shows the smooth curved contour of the elevated dome It is especially recommended that an opaque meal be given, and the film taken with the patient lying on a side In case of hernia this position will facilitate the passage of some of the barium into the pouch above the diaphragm

Some part of the bowel was found displaced in all cases of right sided eventration studied roentgenologically with the opaque meal Thus in Bayne-Jones'¹⁰ case the transverse colon was displaced, looped, and doubled on itself in the right upper quadrant The liver, however, was found high up under the ribs, and covered by the diaphragm In Aronson's⁵ case the dilated colon was in the right chest above the liver and covered by the diaphragm The proximal colon was anterior to the liver and under the right diaphragm in the case described by Golob¹⁴ Morris'¹⁶ case had the stomach under the right diaphragm Our case, too, had bowel in the right thorax situated right under the diaphragm Finding the displaced bowel in the right chest and under the elevated diaphragm, weakens the argument of those who assert that in congenital eventration it is the liver that is invariably found under the diaphragm¹⁵

Measurements of changes in the intragastric pressure during respiration have been used by some to differentiate between hernia and eventration of the diaphragm. Hildebrand and Hess²³ used this method in their case and their diagnosis was confirmed by autopsy. They demonstrated an inspiratory rise and an expiratory fall in the intragastric pressure, which is the reverse of what should occur if the stomach had invaded the thorax through a hole in the diaphragm. The test, however, is not as valuable as was at first anticipated, for the intragastric pressure has been shown to vary normally with intercostal and abdominal types of respiration.

Most of the instances of eventration require no treatment. However, strenuous exercise should be prohibited. Pregnancy, if it occurs, should not be allowed to go on to labor, but should be terminated by abdominal section. Those who are overweight should aim to reduce. Should troublesome symptoms be present, surgical intervention may be considered. In Leich's case, quoted by Lord, three plaits were taken in the diaphragm through an incision in the outer part of the rectus muscle. The patient improved and seven months after the operation she was entirely relieved of her pulmonary and gastric symptoms.

CASE REPORT

M. L., Jewish, aged 27, married, primipara, housewife, was admitted to the obstetrical ward of the Mount Sinai Hospital (service of Dr. Chas. Newberger) on April 11, 1932.

Because of prolonged labor, exhaustion, and the patient's seeming inability to accomplish anything by "bearing down," forceps were applied and an episiotomy was done. She was sent back to the ward in good condition.

On the following day the intern on the service noticed that the patient was somewhat dyspneic and slightly cyanotic. She also complained of a slight cough. Eliciting definitely abnormal findings in the right chest, he fortunately became alarmed and ordered a bedside roentgenological examination.

The film was shown to us and we suggested that the condition might be an eventration of the diaphragm. The patient was transferred to our service (service of Dr. I. M. Trace) after her puerperium for a detailed study of her abnormality.

History. The pertinent statements in the history were as follows: Moderate shortness of breath upon exertion has been present ever since she can remember. A non-productive cough has bothered her since childhood. When she lies on her abdomen she becomes quite dyspneic, and often begins belching, which relieves her. Indefinite pains in the upper abdomen have been present all her life, which she ascribes to "gas." The pregnancy, however, did not aggravate her condition at all, being entirely symptomless.

There is no history of trauma or accident of any kind, her mother testified to that. During her entire childhood, she could never play as much, nor run as fast as her playmates, because of shortness of wind, and marked fatigability. When one year of age she had three attacks of pneumonia. Her mother could not furnish any more details as to this supposed pneumonia. In all probability, the findings on the side of the eventration were repeatedly taken for pneumonia.

Physical Examination. The patient was lying comfortably in bed, and was neither dyspneic nor cyanotic. The pulse was 80, regular, the temperature 99.2° F rectally, and the blood pressure was 110 mm of mercury systolic and 70 diastolic.

She was short, rather sthenic, and quite obese. The head and neck were not abnormal.

The chest was symmetrical and its antero-posterior diameter seemed enlarged. The inspiratory expansion of the two sides of the chest, except the costal margins, was the same. Litten's sign was not present on the right side.

There was dullness on the right side up to the second interspace anteriorly and up to the midscapular region posteriorly. (However, there were times in the following few years during which we observed the patient, when the dullness anteriorly gave way to a tympanitic note, and sometimes to a hyperresonant note. In view of



FIG 1 Film taken at end of deep expiration. The curved line of the right phrenic leaf is at the lower border of the second rib anteriorly. The contour of the arched line is regular throughout its entire course. The trachea and heart are displaced somewhat to the left.

the roentgenological findings to be described later, the reason for these alterations in the percussion note is clear.) There were no compensatory changes on the left side. The heart dullness extended 11 cm. to the left of the mid-sternal line. No sub-sternal dullness was elicited.

The breath sounds were very distant anteriorly, and were diminished posteriorly over the dull area; deep inspiration increased the breath sounds only slightly. Above this impaired area on the right the breath sounds were normal and were likewise normal over the left chest. There were no râles elicited at any time. Peristaltic

sounds in the right chest were heard while the patient was in the hospital, and several times since in the last few years. These sounds were heard anteriorly as high as the third interspace and about the midscapular region posteriorly. They were much louder anteriorly than posteriorly, and were best heard following an enema or a cathartic. At other times they were not loud, and one had to listen rather intently in order to hear them. The heart sounds were normal, and no murmurs or accentuations were present.

The Hoover Sign. With the patient in the recumbent position the contour of the

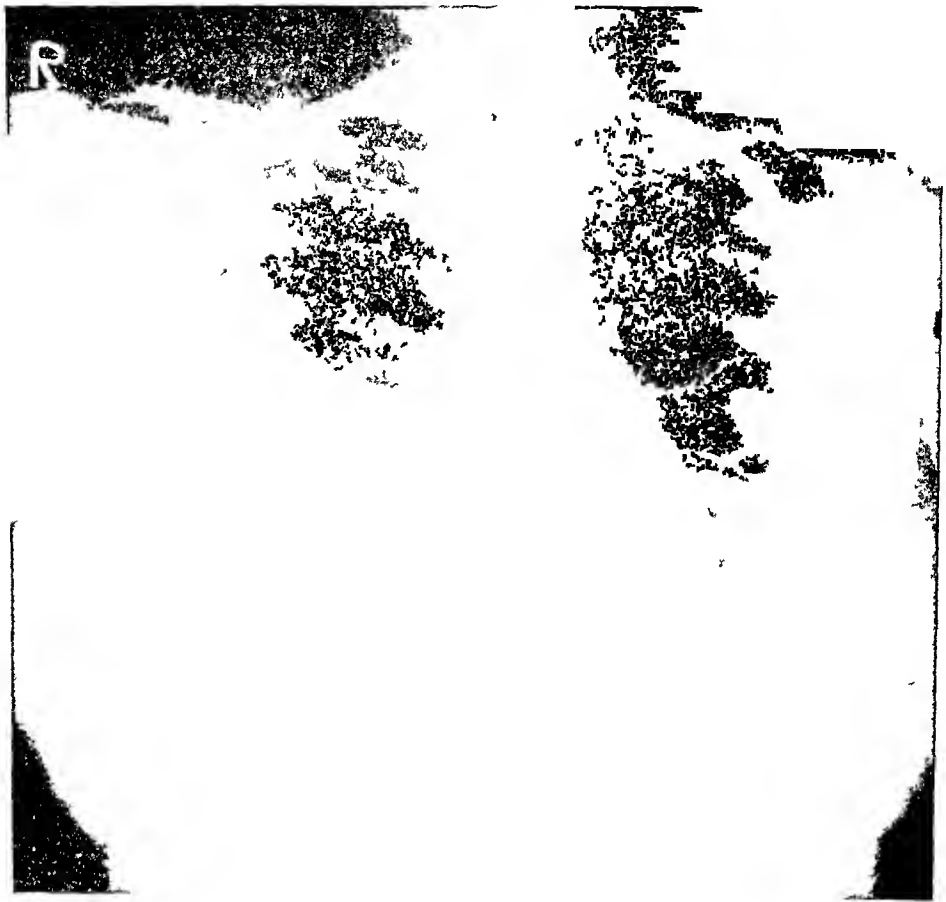


FIG 2 Film taken at end of deep inspiration. The arched line of the right diaphragm is at the lower border of the third rib, thus it has moved one interspace downward during inspiration.

lower chest, the movement of the costal margins, and the excursion of the abdominal wall were studied.

Harrison's groove on the right side was much shallower than on the opposite side where it was quite marked, despite the patient's moderate obesity. This may have been the result of the action of the intercostal muscles on the right side unopposed by the inactivated diaphragm.

The excursion of the abdominal wall with the usual bulging in the epigastrium during inspiration was present on the left side, but absent on the right. This phenomenon is a measure of the excursion of the diaphragm and its absence means



FIG 3 Lateral view of thorax showing the dome of the right diaphragm high above and that of the left far below. Note that the contour of the eventrated diaphragm is regular throughout, and that bowel is situated under it

that one leaf of the diaphragm is inactive. During deep inspiration there was a definite retraction of the right side of the epigastrium.

Inspection of the movement of the costal margin on the right side was not very convincing, as to its exaggerated inspiratory divergence from the median line, probably because of the patient's moderate obesity. However, it was certain that the right costal margin did not move in the same fashion or direction as the left one did, upward and outward.

Palpation of the right costal margin, however, showed definitely that there was an exaggerated inspiratory divergence from the median line. The finger tips were applied to the extreme ends of the ribs forming the costal margin, as suggested by Korns¹³. Thus the Hoover sign was positive in our case.

The abdomen was fairly obese, the liver, spleen, and kidneys were not felt. Percussion of the abdomen revealed dullness of the entire right side. The left side showed a moderately tympanitic note. (This finding has never varied.) Peristaltic sounds were few and always limited to the left side. There was no tenderness.

Laboratory Findings The urine was normal. The blood showed a slight degree of hypochromic anemia. The Wassermann and Kahn tests were negative. The electrocardiogram was essentially normal.

Röntgenologic Examination The film taken at the bedside, which suggested to us eventration of the diaphragm, showed the typical curved line of the right phrenic



FIG 4 Film taken immediately after a barium meal. The stomach is in its normal position. The duodenum is not seen, but when studied under the fluorescent screen it was normally situated and filled out completely. The barium, after leaving the first few inches of the jejunum, shot up into right thorax, instead of turning to the left and downward, as it normally does. The liver and kidney can be discerned in their normal places, and the bowel seems to enter the right thorax anteriorly to the liver.

leaf at the lower border of the second rib anteriorly. The contour of the arched line was regular throughout its entire course. The trachea and the heart were somewhat displaced to the left. The left diaphragm was in its usual position.

Later films were taken of the chest at the end of deep expiration and inspiration. The arched line at the end of the latter phase was at the level of the lower border of



FIG 5 Lateral view of thorax five hours after a barium meal. The latter is seen in the colon with the arched line of the right diaphragm above it. The contour of the curve is not deformed but it is as regular as before (see figure 3), thus speaking for eventration of the diaphragm.

the third rib anteriorly, thus showing how much the diaphragm had moved (figures 1 and 2). The other features were the same as in the first film.

Fluoroscopic examination confirmed the above findings. The right diaphragm was seen to move slightly downward upon deep inspiration and upward during deep expiration. Thus there was no paradoxical movement of the eventrated diaphragm in our case. In the lateral view one could visualize the regular arch of the right phrenic leaf and its slight excursion. The arch of the left diaphragm could also be seen, but at quite a distance below that of the right (figure 3).

Inspiratory excursion of the mediastinum was not present in our case. This sign was looked for on several occasions during the time that the patient was under ob-

servation, and we could never discover the slightest inspiratory deviation of the mediastinum

The opaque meal showed that the esophagus and the stomach were in their normal positions. The stomach was of the fishhook type and without abnormalities. The duodenum was normally situated and filled out completely. The barium, after leaving the first few inches of the jejunum, shot up into the right thorax instead of turning to the left and downward as it normally does (figure 4). After five hours, all of the barium had left the stomach and was seen in the right chest. A lateral view



FIG 6 An opaque enema showing that the cecum, ascending colon, hepatic flexure, and part of transverse colon are situated in the right thorax. Part of the cecum and first portion of the ascending colon are to the left and under the lower half of the sternum. The arch of the diaphragm is only faintly seen above the bowel.

at this time demonstrated the barium in the colon, with the arched line of the diaphragm above it. The contour of the latter was not deformed but remained as regular as before (figure 5). This lateral film was taken with the patient in the recumbent position. These findings speak against a hernia and for eventration of the diaphragm.

An opaque enema demonstrated that the cecum, appendix, ascending colon, hepatic flexure, and part of the transverse colon were situated in the right thorax, above the twelfth dorsal vertebra. The cecum and first part of the ascending colon were a little to the left of the midline and extending to the left side, thus displacing the



FIG 7 A composite picture after an opaque enema showing the entire course of the large bowel. Note the marked displacement of the trachea and heart

trachea and the heart to a still greater degree (figures 6 and 7). When the bowel was distended by the opaque enema, the patient complained of dyspnea, palpitation, and discomfort. She also became slightly cyanotic. It is entirely possible that the symptoms that aroused the curiosity of the intern in the obstetrical ward were due to the morning enema.

The liver and kidneys were seen to be in their normal position (figure 4). Pyelograms showed the kidney pelvises to be normal.

COMMENT

The roentgen-ray findings showed that the intestinal tract between the first portion of the jejunum and the second portion of the transverse colon was extruded into the right thorax, and lay between the diaphragm above and the liver below. In this respect our case differs from the description of most of the reported cases in which it has been more usual to find the liver high up under the eventrated diaphragm.

Our patient has no bowel in the right side of the abdomen. Should she ever develop an attack of appendicitis, her symptoms would certainly be atypical and the method of surgical approach would have to be extraordinary indeed.

The patient has been under observation for the last few years. She feels quite well except for the slight discomforts mentioned above. Should she become pregnant again, an abdominal section will be strongly urged before labor sets in.

CONCLUSION

A case of right-side "eventration" is added to the literature, thus raising the number of reported cases to ten.

The diagnosis in this case was made because of the following findings:

- (1) High position of the right diaphragm
- (2) Regular contour of the arched line as seen in the anteroposterior and lateral views
- (3) Definite, although limited, excursions of the elevated diaphragm
- (4) Roentgen-rays after an opaque meal and after a barium enema, with the patient in the recumbent position, showed that the arched line was the dome of the diaphragm, and not the outline of a distended bowel
- (5) Evidence of inactivation of the right half of the phrenic leaf (Hoover's sign)

The extruded bowel was situated between the right diaphragm above and the liver below, a finding unlike that in most cases reported.

REFERENCES

1. WOOD, W. B., and WOOD, F. G. Congenital elevation of diaphragm, *Lancet*, 1931, ii, 392-397.
2. THOMAS, R. Vier Fälle von Hernia diaphragmatica, *Arch. f. path. Anat.*, 1882, lxxviii, 515-555.
3. DOERING, H. Über Eventratio diaphragmatica, *Deutsch. Arch. f. klin. Med.*, 1902, lxxii, 407-414.
4. FALKENSTEIN, quoted by BECK, C. H. Eventration of diaphragm, *Ann. Clin. Med.*, 1923, i, 362-371.
5. ARONSON, E. A. Hirschsprung's disease with eventration of right half of diaphragm, *New York Med. Jr.*, 1918, cviii, 196.
6. CHRISTIAN, H. A. Eventration of the diaphragm, in OSLER, W., and McCRAE, T. *Modern medicine*, Ed. 3, 1925, Lea and Febiger, Philadelphia, p. 344.
7. PETIT, J. L. *Traité des maladies chirurgicales et des opérations qui leur conviennent*, 1774, T. F. Didot, Paris.

- 8 CRUVFILIHER Traite d'anatomie pathologique generale, 1849, Tome I, Bailliere, Paris, pp 614-617
- 9 BAMBERGER Ergebn d inn Med u Kinderh , 1913, xii, 327
- 10 BAYNE-JONES, S Eventration of the diaphragm with report of right sided eventration, Arch Int Med , 1916, \vii, 221
- 11 GLASER, F Über Eventratio diaphragmatica, Deutsch Arch f klin Med , 1903, lxxviii, 370-379
- 12 HIRSCH, C Zur klinischen Diagnose der Zwerchfell-hernie, Munchen med Wchnschr , 1900, \lvii, 996-999
- 13 KORN, H M Diagnosis of “eventration” of diaphragm, Arch Int Med , 1921, \xviii, 192
- 14 GOLOB, M Right diaphragmatic eventration accompanied by cardiospasm as reflex of malignancy at cardia, Med Jr and Rec , 1926, cxxiv, 473-474
- 15 FATOU, PREVOST, L, and PRUVOST, F Un cas d'eventration diaphragmatique droite, Bull et mem Soc med d hop d Par , 1928, lii, 259-268
- 16 MORRIS, H Eventration of the diaphragm, British Jr Radiol , 1929, ii, 85
- 17 BLACKFORD, L M, and BOOTH, W T Dextrocardia secondary to eventration of diaphragm, report of asymptomatic case, Jr Am Med Assoc , 1932, \xcviii, 883-885 (Quoting a case of Dr R A Bartholomew)
- 18 LORD, F T Eventration of diaphragm, Arch Surg , 1927, xiv, 316-329
- 19 HOOVER, C F Diagnostic significance of inspiratory movements of costal margins, Am Jr Med Sci , 1920, clxx, 663
- 20 WALTON, H J Eventration of diaphragm, Am Jr Roentgenol , 1924, xi, 420-426
- 21 ASSMANN, H Quoted by KORN, H M¹³
- 22 MOORE, A B, and KIRKLIN, B R Progress in roentgenologic diagnosis of diaphragmatic hernia, Jr Am Med Assoc , 1930, xcvi, 1966-1969
- 23 HILDEBRAND, H, and HESS, O Zur Differential-diagnose zwischen Hernia diaphragmatica und Eventratio diaphragmatica, Munchen med Wchnschr , 1905, lii, 745-748

CASE REPORTS

INSTANT DEATH IN BACTERIAL ENDOCARDITIS REPORT OF A CASE WITH MYCOTIC ULCERATION OF THE CONDUCTION SYSTEM *

By JOHN G KIDD, M D, *Detroit, Michigan*

SUDDEN death, as it occurred in the present instance, is not the rule in subacute bacterial endocarditis. Such unexpected death contrasts sharply with the usual protracted course of this disease, so ably described by the late Dr. William Sidney Thayer in his remarkable monograph¹

The disease is often distressingly chronic. Days and weeks and months pass by—every day with its morning of hope and its evening of depression. And the fatigue and the fever and the anorexia continue—moments, days, even weeks of apparent improvement and elation fatally dispelled by ever-recurring aggravations of first one, then another symptom. And slowly and surely the patient loses ground. The anemia increases. Evidences of myocardial insufficiency are added to the symptoms of chronic sepsis. The complexion assumes the peculiar, earthen greyish color, insisted on by Libman. With the advancing renal changes, the anorexia becomes more obstinate, and there is often nausea and vomiting. Edema of the face and dependent parts sets in. Profoundly enfeebled, with pale, grey, anxious face, puffy, transparent eyelids, inert, waxy bulbous fingers, the patient is harassed by transient hallucinations of vision which he recognizes as hallucinations but cannot escape, by the dyspnea depending in part on the sepsis, in part on the anemia, in part on the nephritis, in part on the myocardial weakness, by the constantly recurring painful cutaneous or splenic emboli, by the persistent and unconquerable nausea. The least movement exhausts him, the nightly sweats weaken him, he is so tired! The very attentions of the nurse annoy him. And then, so often, as if to crown his ills, a sudden hemiplegia with flaccid arm and leg and drooping mouth and open eye. Finally, with wrinkled forehead and careworn face, he sinks into a troubled sleep and breathes his last—the victim of chronic sepsis, or myocardial weakness, or nephritis, or a terminal pneumonia, or cerebral embolism—or all.

In this paper photographs describe the anatomical lesions responsible for instantaneous death and the probable mechanism of death is discussed. Four similar cases previously described in the literature are cited.

REPORT OF CASE

Summary R. K. N., admitted August 18, 1932, died August 25, 1932. A boy of 18 complained of "rheumatism and heart trouble" recurring in attacks since the age of four. History, physical findings, and positive blood culture pointed to the diagnosis of subacute streptococcal endocarditis on the basis of old rheumatic heart disease. Remittent fever of 101 to 102 degrees daily was followed by unexpected instantaneous death on the eighth day after admission. At autopsy a large mycotic ulceration which

* Received for publication August 14, 1934.

From the Department of Medicine of the Henry Ford Hospital.

had almost perforated the ventricular septum was found occupying the site of the a-v node

History (Obtained from the patient and his mother) At the age of four the patient had an attack of "rheumatism" which laid him up for two months. During this attack the elbows, wrists, fingers, knees and feet were swollen, tender and painful at one time or another. Just as the joint symptoms began to subside, extreme palpitation, dyspnea, and weakness were noted. These symptoms were attributed to heart disease by a physician at the time, and the patient stated that he had had them periodically since. Following this episode he was a delicate child, having frequent colds and attacks of sore throat until the age of nine, when he began to improve and entered school. For the next four years he was fairly well, and was able to do his work without interruption. At the age of 14 he won the high jumping championship of his class at school but while participating in a track meet he became chilled, a sore throat developed, and he spent the next several weeks in bed because of palpitation, dyspnea, and weakness. About a year later the patient missed a semester from school because of the same symptoms, and he was confined to bed in a hospital for 18 days during this period. Following this bout, however, he was fairly well until the onset of the present illness.

The immediate present illness began in March 1932, four months prior to admission to the hospital, when the patient was confined to bed for two weeks with an acute upper respiratory infection and fever which was diagnosed influenza. After this episode he was unable to attend school or to work because of weakness and dyspnea. One month before entry he again noted pain and swelling of the joints, mainly the left knee, left hip, and both ankles. These symptoms persisted until his entry, and during this month he lost five pounds in weight. On several occasions in the few weeks preceding admission, he had noted a precordial sensation of irregularity in his heart beat, and once, about two weeks prior to admission, while walking across a room, he stopped abruptly, grasped his precordium and exclaimed, "my heart stopped!" He became dizzy and felt faint, but the attack passed off a few minutes after he sat down. About 10 days prior to admission the patient and his mother noted the spontaneous appearance of several irregular purplish spots, resembling bruises, about the size of a silver quarter, near the left ankle.

Physical Examination Temperature 99, pulse 100 and respirations 28. Weight 116 pounds—estimated ideal weight 156 pounds. The patient was a tall, emaciated boy of about 18 years who appeared sick and weak and uncomfortable. He had a subicteric pallor and was short of breath. There was no cough or cyanosis. Pulsation of the precordium and carotid vessels was striking and the whole bed oscillated with each heart beat. Petechiae were noted in the right conjunctival sac. The apex impulse of the heart was diffuse and heaving and located in the anterior axillary line. A short thrill, systolic in time, was palpated over the base of the heart. The area of cardiac dullness extended 14 centimeters to the left of the midsternal line in the fifth interspace and six centimeters to the right in the fourth interspace. The heart tones were regular and accelerated. The first sound at the apex was almost completely obscured by a harsh prolonged systolic blow which radiated outward into the axilla. A short presystolic murmur was also heard in this area. At the base of the heart very loud and distinct to and fro murmurs were heard. The blood pressure was 124 systolic and 30 diastolic. The radial pulse was regular and had a slapping, quick quality. The lung fields were resonant everywhere, the bases were on a level and descended about equally, no râles were heard anywhere. The abdomen was flat and soft, the liver and spleen were not felt, and there was no bulging or shifting dullness in the flanks. The extremities showed no edema and the joints appeared normal.

Laboratory Examinations Blood Wassermann negative (Kolmer technic),

Kahn test negative, non-protein nitrogen 27 mg per 100 cc, icterus index 12.5 Red cells 3,500,000, white blood cells 11,100, with 80 per cent polymorphonuclear cells Hemoglobin 9.9 grams per 100 cc In the blood culture, many colonies of gram positive cocci appeared on the second day These were later defined as streptococci of the viridans group The urine was dark reddish brown, specific gravity 1.020, it contained a moderate amount of albumin, and there were red blood cells in moderate number in the centrifuged specimen

Course The temperature ranged from normal to 102° daily The pulse was usually regular but extrasystoles were sometimes noted, and on several occasions coupled beats were felt No digitalis was prescribed and none had been taken prior to admission The pulse rate usually varied between 85 and 120 per minute, on one instance the rate was charted at 56 per minute The patient appeared to gain strength, and aside from the extreme sweating and persistent weakness and dyspnea, he was fairly comfortable On the eighth day following admission a transfusion was given at 10 o'clock in the morning with 500 cubic centimeters of citrated blood taken from patient's brother as donor During the afternoon of that day the patient felt unusually well and commented on his improvement He called attention to the fact that since the transfusion his bed no longer oscillated with each heart beat, which added to his comfort and peace of mind At five o'clock in the afternoon the coupled beats were again noted at the radial pulse, and there had been a steady decline in the pulse rate from 112 at 8.00 a.m. to 76 at 6.00 p.m. At seven o'clock the patient's bed was rolled out on to the porch as usual and the patient was left smoking a cigarette When the nurse returned five minutes later, she smelled the bedclothes burning, and noted that the cigarette had fallen from the patient's fingers to the bed The patient was pulseless and respirations had ceased A convalescing patient nearby had heard nothing to attract his attention When questioned, he had heard no cough or cry and was entirely unaware that anything unusual had happened

Comment In attempting to explain the mechanism of such instantaneous death in a patient who had bacterial endocarditis, several possibilities were considered coronary embolism, medullary embolism, pulmonary embolism, and rupture of the heart The most likely explanation, however, was thought to be the interruption of the conduction impulses by the same infectious process which involved the endocardium, resulting in sudden complete heart block with ventricular standstill or fibrillation and death As will appear, this was found to be the case

Postmortem (Dr A. O. Severance) At autopsy careful search of the blood vessels of the heart, brain, and lungs failed to reveal any emboli or thrombi The findings of chief interest were in the heart, which weighed 640 grams There were extensive warty vegetations on both the mitral and aortic valves as is shown in the photographs Figure 1 shows the extremely large vegetations on the aortic leaflets and on the posterior surface of the mitral leaflets The largest group of vegetations in the center of the photograph measured six by three centimeters and involved chiefly the posterior aortic leaflet and the under surface of the posterior mitral leaflets Note also the rather shallow mycotic ulcerations which involved the endocardium just beneath the posterior aortic leaflet, the areas of greatest involvement and ulceration corresponded identically with the course of the bundle of His and the left branch of the auriculo-ventricular bundle⁹ Figure 2 shows the right auricle and the medial cusp of the tricuspid valve Note a small area (a) just in front of the anterior attachment of the leaflet This represents an ulceration nine millimeters in diameter which had extended entirely through the septum from the larger ulcerated areas beneath the aortic leaflets on the other side Compare the location of this mycotic ul-

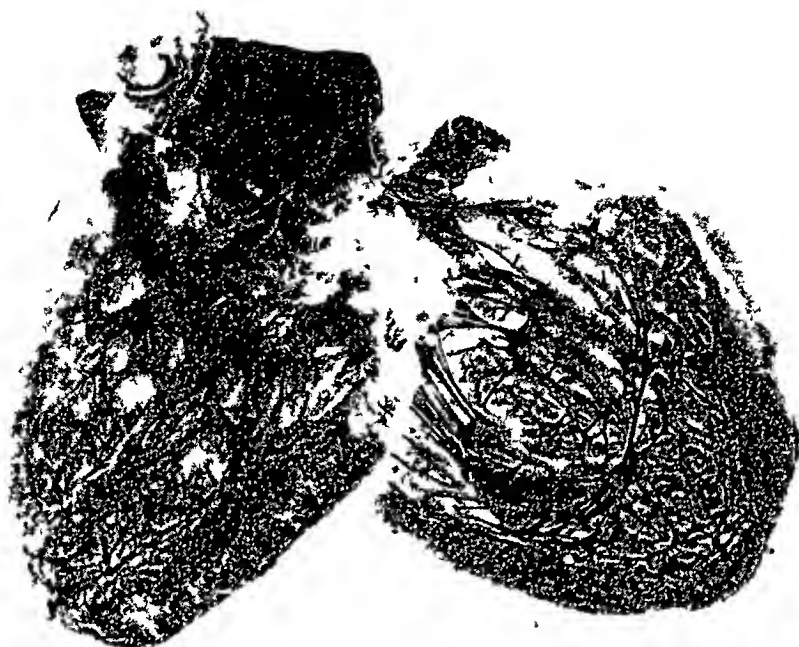


FIG 1 The large vegetations on the aortic leaflets and posterior mitral leaflet are obvious. Note also the sub-endocardial ulcerations beneath the posterior aortic leaflet. These ulcerated areas overlie the course of the left branch of the bundle of His.

ceration with that of the auriculo-ventricular node as illustrated in figure 3, noting the relative positions in the two photographs of the ulceration and Tawara's node, the coronary sinuses, the fossae ovale, and the medial tricuspid leaflets. The corresponding positions of the ulceration and Tawara's node are striking.

REVIEW OF THE LITERATURE

Inflammatory lesions and degenerative processes interfering with the conduction of impulses through the junctional tissues have been cited in numbers. Rosenthal² has recently called attention again to the occurrence of acute isolated myocarditis in which the suppurative process may involve the conducting mechanism. He cited two instances which showed clinical signs of heart block and in each the inflammatory reaction involved especially the bundle of His. Both of his cases presented evidence of valvular endocarditis. Thayer¹ commented on the special frequency of mural endocarditis in subacute streptococcal endocarditis, and noted that aneurysms of the valves and perforations as a result of ulceration were relatively common. In a large series, however, he observed no instances where the specialized conducting tissue was involved. Rothschild et al³ observed that inflammatory lesions (Bracht-Waechter bodies) in the myocardium in subacute bacterial endocarditis are frequently inconspicuous and in general are without effect on intraventricular conduction. In a large number of electrocardiograms in patients with endocarditis they observed significant changes in the ventricular (QRST) complex in only one instance. Prolongation of the P-R interval was noted, however, in 10 of the 123 cases. On the



FIG 2 This photograph shows the right auricle and ventricle and the medial cusp of the tricuspid valve. Note an area (a) just above the anterior attachment of the leaflet. This represents an ulceration about 9 mm in diameter which had extended entirely through the septum from the larger ulcerated areas beneath the aortic leaflets.

other hand White⁴ recognizes that bacterial endocarditis may, rarely, be accompanied by severe myocardial ulcerations. He writes "In very rare cases the process may cause an aneurysm in, or a perforation through, the ventricular septum, or from the left ventricle into the right auricle, or even a rupture of the auricular wall, and, also rarely, invasion of the upper ventricular septal region may damage the auriculo-ventricular bundle (of His) to cause heart block." Blumer⁵ noted the frequency with which the mural endocardium is involved in the pathological process in subacute bacterial endocarditis, but emphasized the relatively slight involvement of the myocardium in this disease. In the 150 autopsies he reported, only seven had microscopic evidence of acute infection of the myocardium and in none of these is any special note made of damage to the conduction system.

Mycotic aneurysms of the valves and shallow sub-endocardial ulcerations then, occur quite commonly in subacute bacterial endocarditis but the myocardium is rarely perceptibly damaged in this disease. We have been able to find record of but four cases of bacterial endocarditis in the literature in which gross

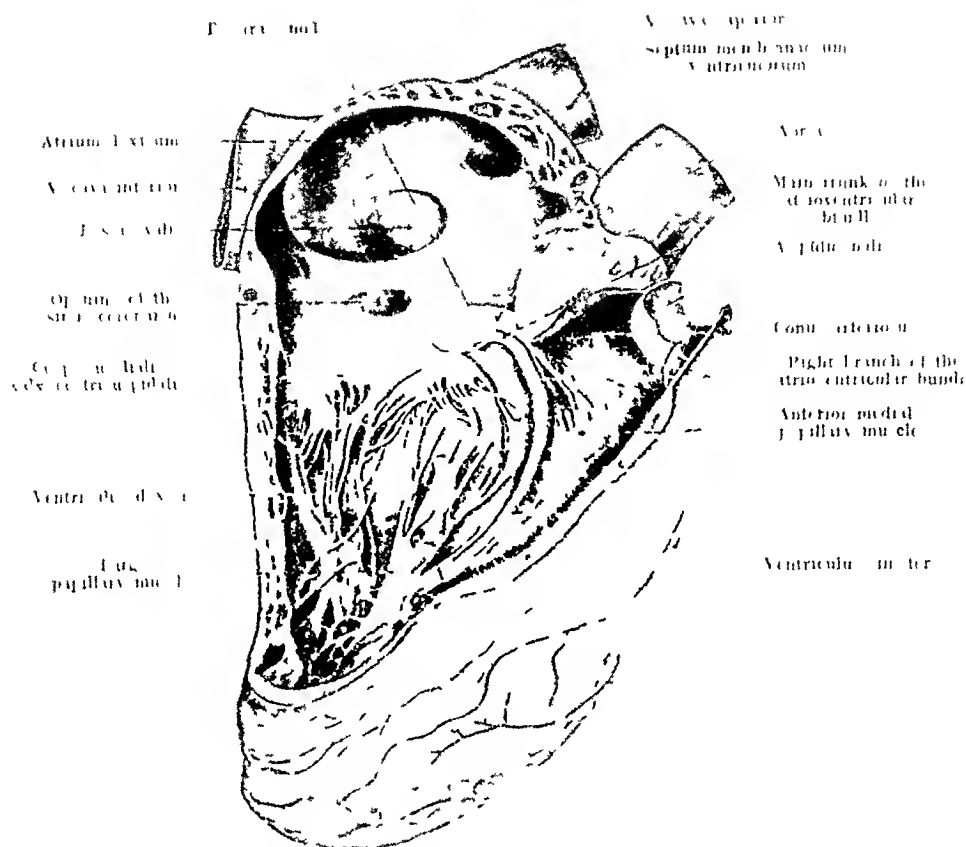


FIG 3 This illustration (reproduced from Spalteholz) shows the location of the a-v node. Compare this illustration with figure 2, noting the relative positions in the two photographs of Tawara's node and the perforating ulceration, the coronary sinuses, the fossae ovalis, and the tricuspid leaflets

mycotic ulceration or aneurysm had interfered with the conducting mechanism*

Wilson⁶ reported three instances of vegetative endocarditis in each of which a mycotic aneurysm involved the interventricular septum. In two of these cases heart block had been diagnosed clinically and the region occupied by the bundle of His was found destroyed by the ulcerating process. Both of these patients died suddenly. Rothschild et al³ reported sudden death in a patient with bacterial endocarditis who had shown electrocardiographic evidence of partial bundle branch block. Necropsy revealed an aneurysm of the sinus of Valsalva caused by the spread of the bacterial infection from the aortic leaflets to the aorta. This aneurysm had projected into the interventricular septum and had partially

* Since this was written Dr Warren Cooksey has called attention to a similar instance in his experience. A middle aged man had an atypical disease suggesting old rheumatic heart disease with a superimposed bacterial endocarditis. Electrocardiograms showed at first a markedly prolonged P-R time. Later the patient developed complete heart block (demonstrated graphically) and died after about three or four days. Autopsy revealed changes characteristic of old rheumatic heart disease and also fresh warty vegetations on the mitral leaflets. Just beneath the posterior aortic leaflet the vegetations had ulcerated through the septum into the right auricle completely destroying Tawara's node. This case was discussed at a State Clinical-Pathological Conference but has not been published.

intercepted the path of the left branch of the bundle of His. Stenstrom⁷ reported a case of bacterial endocarditis in which there was definite clinical and electrocardiographic evidence of heart block on the patient's admission to the hospital. The first tracing showed complete auricular ventricular dissociation with an auricular rate of 73 and a ventricular rate of about 45, the P-R time was 0.45 second. Subsequent tracings showed the block to have disappeared and the P-R time decreased to 0.26 second. The patient had repeated anginal seizures and died suddenly some two months after admission. Sudden death in an anginal seizure was attributed to the necropsy finding of a thrombus in the anterior descending branch of the left coronary artery. Interestingly enough, a healing inflammatory lesion, of the same nature as the fresh endocarditis was found localized in the tissue of the auriculo-ventricular node and the bundle of His. A correlation was noted between the stage of healing of this lesion and the previous functional recovery of conductivity as shown in the electrocardiograms.

SUMMARY

Instant death in a patient with subacute streptococcal endocarditis is described. At autopsy a large mycotic ulceration was found to have eroded through from the left ventricle into the right auricle, largely destroying the region occupied by Tawara's node. Other sub-endocardial ulcerations intercepted the path of the left branch of the bundle of His. Instant death in this patient was thought to be due to the sudden onset of heart block followed by ventricular asystole or fibrillation.

REFERENCES

- 1 THAYER, W. S. Studies on bacterial (infective) endocarditis, *Johns Hopkins Hosp. Rep.*, 1926, **XXII**, 1-184.
- 2 ROSENTHAL, S. R. Branch arborization and complete heart block, *Arch. Int. Med.*, 1932, **1**, 730-758.
- 3 ROTHSCHILD, M. A., SACKS, B., and LIBMAN, E. Disturbances of cardiac mechanism in subacute bacterial endocarditis and rheumatic fever, *Am. Heart Jr.*, 1927, **II**, 356-374.
- 4 WHITE, P. D. *Heart disease*, 1931, Macmillan, New York, p. 350.
- 5 BLUMBERG, G. Subacute bacterial endocarditis, *Medicine*, 1923, **II**, 105-170.
- 6 WILSON, C. P. Mycotic aneurysm involving intraventricular septum, *Am. Heart Jr.*, 1926, **1**, 703-706.
- 7 STENSTROM, N. Recovery from complete a-v block in case of endocarditis with post-mortem examination, *Acta med. Scandinav.*, 1927, **LXVII**, 185-188.
- 8 SPALTEHOLZ, W. *Hand-atlas of human anatomy*, 1923, J. B. Lippincott, Philadelphia, 5th ed., **II**, p. 389a.
- 9 LEWIS, T. *Mechanism and graphic registration of the heart beat*, 1920, Paul B. Hoeber, New York, pp. 4-5.

SPLenic VEIN THROMBOSIS AND ITS RELATIONSHIP TO BANTI'S SYNDROME, WITH REPORT OF A CASE*

By HARRY D LEINOFF, M D, *Bronx, New York*

THE relationship between splenic vein thrombosis and Banti's disease has been much discussed and, like most unsettled questions, it is possible that the cause of disagreement lies in the different conceptions of what actually constitutes Banti's disease. On the one hand, many prefer to speak of the Banti syndrome and thereby testify to their belief that it is a group of symptoms and pathologic changes which may have several pathogenic factors. Among these factors they would include splenic vein thrombosis as primary. Others largely agree with Banti in his conception of a disease which progresses through the stages as described by him and is marked by pathologic changes which include splenic thrombophlebitis, not however as a primary factor. For several years many writers have suggested that the latter may occur independently of Banti's disease and that it may give rise to symptoms which indicate the diagnosis. A review of literature, however, leaves one with the impression that splenic vein thrombosis is an important part of the disease originally described by Banti. The following report illustrates the difficulty of diagnosis in those cases in which hematemesis is the outstanding feature.

CASE REPORT

The patient was a white woman, 28 years old, who was admitted to the hospital on September 23, 1933, complaining of severe epigastric pain, vomiting of blood and a bloody diarrhea. On the day preceding her admission, she had been in comparatively good health and had gone to work as usual, a few hours later she experienced a severe pain in the stomach, vomited a great deal of bright red blood and passed some fresh blood in her stool. She was taken to a local hospital where a diagnosis of bleeding gastric ulcer was made. An operation was advised but was refused. She placed herself under the care of a local physician who treated her for bleeding ulcer, using sedatives and ice bags. Under this treatment her symptoms subsided. The next morning on attempting to rise, she was again seized with severe abdominal pains, vomited blood and was then admitted to the Flower Hospital.

Her illness seems to have started in 1921, approximately 12 years before. At that time, she began to have fainting spells, at least one a day, she would become unconscious and while in this state, blood gushed freely from her mouth. Invariably this bleeding stopped before she regained consciousness. After these attacks, the patient complained of severe substernal burning, so much so that for a time she was treated for "heart burn," but without relief.

On February 27, 1924 while visiting a midwestern town, she complained of a pain in the stomach and fainted, while in this state she was rushed to a hospital and operated on. The surgical report was as follows: "The uterus, tubes and ovaries were normal in size and position. The appendix was turned on itself and bent in midposition and had several adhesions. It was five inches long, congested and thickened. Pathological diagnosis: chronic appendicitis."

The patient had rather a stormy recovery, remaining in the hospital for six weeks. During this time she complained of substernal burning, epigastric pain and the vomiting of blood. Seven months later, on her return to New York the patient

* Received for publication December 28, 1934.

From the Department of Medicine at Flower Hospital, Dr. P. J. R. Schmah's Service.

was operated on for bleeding ulcers. Following this operation all of her symptoms were so aggravated that four months later another operation was performed, and again the patient found no relief. Unfortunately a report of the last two operative procedures was not obtained.

Her hematemesis, epigastric pain, fainting spells and general weakness became steadily worse and on September 8, 1925 she reentered the same midwestern hospital for further treatment. On the day of her admission she was transfused and four days later another operation for recurrent gastric ulcers was done. This operation was reported to me as follows: "An old median scar was excised. There were dense adhesions of the omentum to the abdominal wall. All adhesions were separated and the stomach examined. The duodenal-pyloric junction was thickened. The ulcer scar was found at the greater curvature just above the entrance of the circulation. This ulcer was excised and the wound closed with double linen sutures. A short loop posterior gastro-enterostomy was done."

Again instead of getting better, the patient's condition became definitely worse. She was now unable to retain anything, vomiting blood and food almost continually. On December 5 another laparotomy was performed, of which the following summary report was obtained: "A midline incision was made and the old postoperative adhesions were broken down. The stomach was brought into the operative field and the old gastro-enterostomy scar excised. The stump of the intestines was sutured. Incision of the stomach sutured, the jejunum was replaced in normal position. Stomach opened and bleeding ulcer excised." Laboratory diagnosis: "Minute ulcers upon the duodenal mucosal surface, partially healed." This last operative procedure again failed to give the desired therapeutic results. It is interesting to note that during the last three operative procedures, the patient was pregnant and finally delivered a full term living child. Her symptoms continued with some modifications until the time of her present admission.

The past history of the patient brought out some very interesting points. She had had most of the childhood diseases, namely, diphtheria, chicken pox, scarlet fever, whooping cough and broncho-pneumonia.

On further questioning, the beginning of her illness was featured by the vomiting of bright red blood, burning sensation and occasionally a bloody diarrhea. Later a pain developed as an important symptom. This pain was first located in the epigastrium, was very sharp, had no relation to food, and was associated with a large tender lump in the left hypochondrium. After the vomiting of blood, the pain and the mass would tend to disappear, leaving only a sensation of soreness. The patient complained of profuse menstrual flows and dates all her trouble from the time her menses became profuse. Her fainting spells in the beginning of her illness were associated with hematemesis. About two years before her admission, there was a period of repeated chills, fevers and sweats, during which time she was treated for malaria without any relief. There had been a moderate loss of weight. She also complained of bruising very easily, so that at all times she showed subcutaneous hematomas. The family history was not remarkable.

On physical examination she was moderately well nourished, and revealed little of interest other than the findings in the abdomen. The abdomen showed the scars of the previous operations and was very sensitive throughout, both to light and deep pressure. There was some rigidity of the epigastric region, the lower margin of the spleen was palpable just below the costal margin. The liver was not palpable or enlarged. The pelvic examination revealed a chronic vaginitis and endocervicitis. The lower extremities showed numerous ecchymotic areas.

For a month following admission to the hospital the temperature, pulse and respirations were normal. Then chills, fevers and sweats developed and lasted for five weeks. The fever at times reached 104.5° F with daily remissions.

Laboratory Studies The vomited blood was bright red in color and faintly acid in reaction, suggesting that it might be coming from the esophagus or the upper part of the stomach

Blood examination The red blood cells numbered 3,750,000, the hemoglobin was 81 per cent and the color index 0.8 The white blood cells numbered 9,800, with polymorphonuclear neutrophils 60 per cent, eosinophils 4 per cent, lymphocytes 33 per cent and mononuclears 3 per cent The platelet count was 220,000 on admission, and 115,000 the day after The coagulation time was 5 minutes, the bleeding time 3.5 minutes, and clot retraction was marked within 3 hours

There can be no doubt of the importance of the platelet count in this condition In this case the count was made almost daily and in a general way it was noted that epigastric pain and hematemesis were more apt to occur when the platelet count had fallen to lower levels (table 1)

TABLE I
Relation of Platelet Count to Clinical Symptoms

DATE	PLATELET COUNT	SYMPTOMS
9-23-33	220,000	severe pain
9-25	115,000	severe pain
9-26	125,000	comfortable
9-28	135,000	comfortable
9-29	120,000	severe pain, hematemesis
9-30	135,000	severe pain, hematemesis
10-2-33	185,000	comfortable
10-9	205,000	comfortable
10-11	225,000	comfortable
10-18	190,000	severe hemorrhage
10-20	130,000	pain
10-23	115,000	pain
10-25	160,000	pain
10-31	140,000	pain
11-3	135,000	pain
11-6	170,000	pain
11-10	160,000	pain
11-13	225,000	pain, bleeding
11-17	200,000	comfortable
11-20	200,000	comfortable
11-22	operation	
11-27	265,000	no complaints
12-11	445,000	no complaints
1-13-34	300,000	no complaints

During the febrile period repeated blood cultures yielded no growth Blood smears examined for both malarial and filarial parasites were negative The Widal and Felix-Weil reactions were also negative

The blood Wassermann reaction was one plus, but the Kahn reaction was negative Blood chemistry creatinine, 1.5 mg, urea, 20.0 mg, blood sugar, 109 mg, uric acid, 4.0 mg, calcium, 10.6 mg

The urine showed numerous pus cells associated with *Trichomona vaginalis* Roentgen-ray studies of the chest showed normal heart and lung shadows with a clear retro-cardiac space The gastrointestinal series did not show any filling defects which might suggest an ulcer, though there was some barium retention in the stomach five hours after the beginning of the series On November 20, 1933 esophagoscopy revealed two well formed varices present in the cardiac end of the esophagus

In the foregoing the following might be emphasized (1) The length of duration of symptoms, and their persistence following numerous surgical attacks on supposed peptic ulcer, (2) The pain in the epigastrium which was relieved by the vomiting of bright red blood, (3) The enlarged spleen, which grew larger just before an attack of pain and then decreased in size after the vomiting of blood, (4) The tendency to bruise easily, associated with a rather low platelet count, (5) The occurrence of chills, fevers and sweats, (6) The presence of esophageal varices

In attempting to make a diagnosis in this case the possibility of peptic ulcer seemed unlikely because of the lack of roentgen-ray evidence, the persistence of symptoms after operation, and the atypical pain which had no relation to food but was relieved by the vomiting of faintly acid blood. Purpura hemorrhagica was eliminated by the normal bleeding, coagulation and clot retraction time, in spite of the presence of a relatively low platelet count and a palpable spleen. The severe substernal burning made us consider heart disease, but not seriously after the negative physical examination and the negative roentgen-ray findings in the chest. The chills, fevers and sweats occurring with regularity, and the presence of an enlarged spleen suggested chronic malaria, but repeated blood smears were negative.

Consideration of the history and examination suggested that possibly some interference with the return circulation of the spleen might account for the whole disorder. Such an obstruction would cause an increase in the collateral circulation through the short gastric veins leading to the formation of esophageal varices, and whenever the burden on the splenic circulation increased, the spleen would enlarge, causing an increased pressure in the varices which clinically might manifest itself as pain. Rupture of the varices would relieve this pain, and the patient would feel better. After healing of the ruptured varix, and restoration of blood volume the process would start over again. The causes of such an obstruction include thrombosis of the splenic vein due to unknown causes, a tumor pressing on the splenic vein, post-operative adhesions, a diffuse generalized fibrosis of the reticular system of the spleen, or a thrombophlebitis of the splenic vein. Because of the associated chills and fevers in this case, the latter was thought to be the cause, though it was considered possible that postoperative adhesions played a very important part. Thrombophlebitis having been agreed on as the most likely possibility, splenectomy was performed on November 22, 1933, and was followed by an uneventful recovery. The patient had no unusual abdominal pain following the operation.

Three months after the operation the patient was completely free of gastric symptoms. The vomiting of blood, the pain and substernal burning had stopped. Her general health was excellent. Immediately after the operation the platelet count rose to 445,000, the coagulation time four and one-half minutes, and the clot retraction was marked within seven hours. A blood count taken about two months after splenectomy showed red blood cells 3,770,000, hgb 77 per cent and color index 1.0. White blood cells 10,900, with polymorphonuclear neutrophils 51 per cent, eosinophiles 2 per cent, lymphocytes 44 per cent, and mononuclears 3 per cent. The platelets numbered 300,000.

Dr. Earl Eaton, who performed the operation, remarked that he found multiple adhesions of the stomach and greater omentum to the anterior abdominal wall and liver in the upper right quadrant. The gall-bladder, duodenum and pylorus were covered by adhesions. The fundus uteri was adherent to the sigmoid by dense bands. The liver appeared normal, the gall-bladder thin-walled, emptied readily, and contained no stones. The stomach showed several scarred areas on its lesser curvature and anterior wall. The spleen was three times its normal size and showed areas of fibrosis throughout. The veins toward the stomach were large and varicose.

The pathologic examination of the excised spleen was carried out by Dr. W. E. Youland who made the following report. The spleen measures 10 by 7 by 2 cm. It is fairly firm. On section considerable blood exudes. The venous channels are somewhat dilated. The Malpighian corpuscles stand out prominently, and the intervening tissue is dark reddish in color. Microscopic sections show dense cellular elements in the splenic interstices. A part of this cellular picture undoubtedly includes a marked hypertrophy of the endothelium of the sinusoids. It is impossible to identify with accuracy the type of cells present, except for a preponderance of eosinophiles which are scattered uniformly throughout the entire section. The sinuses are widely dilated. There is a considerable numerical increase in the lymph-

phoid follicles. Virtually all of the follicles present appear to be inactive. In some of the follicles there is a definite and in some, a marked increase in the number of lymphoblasts. In many follicles a homogeneous eosinophilic substance is present in the form of irregular anastomosing strands, resembling somewhat early formed amyloidosis. The central arterioles of the follicles as well as arterioles throughout the splenic tissue appear to be definitely thickened with a narrowing of the lumen. There are other areas showing a thinning out of the cellular element with apparently an increase of reticular fibrosis. The interstitial tissue throughout the sections as a whole suggests slight thickening, some sections showing more definitely fibrotic changes than others. The lymphoid follicles in other sections show a marked increase of red blood cells which may be considered as due to capillary congestion or possibly to erythrocytic infiltration. Oil immersion examination shows no definite phagocytosis of red blood cells. There are no megalokaryocytes present. The large blood vessels, especially the vein suggests a possible fibrous replacement of the wall and also some dilation. No other definite changes can be made out.

DISCUSSION

As to the etiology of splenic vein thrombophlebitis very little can be said. It occurs in children.⁶ Trauma may play an important part. Abdominal tumors which obstruct the flow in blood vessels, or local areas of degeneration and inflammation may be causative agents. Postoperative adhesions may also contribute. It has been suggested that physico-chemical factors in the splenic vein might in a way be responsible. Alteration in the platelet count can precipitate the so-called platelet crisis and lead to thrombus formation, as suggested by Rosenthal.⁷

There can hardly be doubt that a thrombus in the splenic vein can produce the clinical picture which has been described as characteristic of thrombophlebitis of the splenic vein. The report by Frick,⁸ with the associated autopsy findings is important in this connection. On the other hand Warthin¹⁰ and McMichael³ have been unable experimentally to produce this picture in laboratory animals, and Wohlwill⁹ showed that the presence of a definite thrombus in the splenic circulation did not necessarily produce an enlarged spleen.

The original writings of Banti,¹ quoted by Warthin¹⁰ suggested that splenic or portal vein thrombosis was a constant factor in Banti's disease and it is because of this factor that these two conditions were thought to be the same.

On the other hand Vertan,¹⁰ McMichael,³ Evans,¹¹ and Bryce¹² though describing a clear cut clinical picture of Banti's disease, have been unable to find definite evidences of thrombosis in the splenic circulation and therefore have suggested that thrombophlebitis of the splenic vein is entirely different from Banti's disease. The failure of these investigators to find the splenic vein lesion might be explained by the fact that practically all of their work has been done on spleens which were removed at operation and most of these workers did not thoroughly investigate the splenic and hepatic circulations. Moschowitz¹³ attempted to show that Banti's disease was in reality a complex syndrome wherein any one stage of the disease might dominate the clinical picture. Microscopic studies in splenic vein thrombophlebitis have shown a marked resemblance to the splenic picture of real Banti's. There is a moderate proliferation of the reticulo-endothelial system with some dilation of the sinuses. The Malpighian corpuscles show some fibrosis of the central artery, and some hyaline changes, and though endophlebitis is rare, it is occasionally seen. The blood vessels show

some fibrosis, and a narrowing of the lumen. An occasional siderotic nodule is present indicating hemorrhage.

The symptomatology of splenic vein thrombophlebitis is characterized by chronicity, gastric distress and hemorrhages, an enlarged spleen, and symptomatic relief after the vomiting of blood. A mild anemia and the demonstration of esophageal varices help to make the diagnosis certain. Because of the multiplicity of symptoms which these patients present, a careful differential diagnosis must include a consideration of peptic ulcer, hemorrhagic diseases, heart disease, chronic malaria, parasitic diseases of the spleen, and advanced Banti's disease.

The prognosis is poor in untreated cases, as the patient will eventually die from a severe hemorrhage. Following splenectomy recovery and comparatively good health usually result.¹⁴ The preoperative platelet count is important.¹² It has been shown⁷ that where the count is high the mortality of splenectomy is markedly increased, the patients usually dying of a massive portal thrombosis, probably related to the tremendous rise in the platelet count following operation. Preoperative transfusion is of course indicated in very anemic patients.

CONCLUSIONS

- 1 Splenic vein thrombosis is essentially a phase of Banti's disease.
- 2 It is characterized by chronicity, an enlarged spleen, vomiting of blood which gives symptomatic relief, a moderate anemia and esophageal varices. The splenic tumor decreases in size after a hemorrhage.
- 3 It is amenable to surgical removal of the spleen.
- 4 The surgical risk is in direct proportion to the platelet count, the higher the count, the poorer the prognosis.

REFERENCES

- 1 BANTI, G. Quoted by Warthin¹⁶
- 2 GRAY, H. Anatomy of the human body, 1930, Lea and Febiger, Philadelphia.
- 3 McMICHAEL, J. Local vascular changes in splenic anemia, *Edinburgh Med. Jr.*, 1931, *XXXVIII*, 1-29.
- 4 HERTHIMER, G. *Berlin klin. Wchnschr.*, 1917, 82.
- 5 BOYD, W. Surgical pathology, 1933, W. B. Saunders Co., Philadelphia.
- 6 SMITH, R. M., and HOWARD, P. J. Early occurrence of gastric hemorrhage in children with splenomegaly, *Am. Jr. Dis. Child.*, 1927, *XXIV*, 585-594.
- 7 ROSENTHAL, N. Clinical and hematologic studies on Banti's disease, *Jr. Am. Med. Assoc.*, 1925, *LXXXIV*, 1887-1891.
- 8 FRICK, A. Chronic splenomegaly, *Jr. Am. Med. Assoc.*, 1922, *LXXVIII*, 424-425.
- 9 WOHLWILL, F. Über Pfortadersklerose und Bantinihnliche Erkrankungen, *Virchow's Arch. f. path. Anat.*, 1925, *ccliv*, 243-271.
- 10 VERTAN, E. Bericht über einen durch Milz Venenthrombose bedingten Fall von Splenomegalie, *Zentralbl. f. Chir.*, 1930, *LII*, 1342-1344.
- 11 EVANS, W. H. Blood platelets in splenic anemia, with special reference to treatment by splenectomy, *Lancet*, 1929, *i*, 277-282.
- 12 BRYCE, A. G. *Lancet*, 1932, *VI*, 1423-1425.
- 13 MOSCHCOWITZ, E. Banti's disease, *Jr. Am. Med. Assoc.*, 1917, *LXI*, 1045.
- 14 OSIFER, W. H. Modern medicine, Vol. 3, 1925, Lea and Febiger, Philadelphia.
- 15 ROLIFSTON, H. D. Chronic splenic anemia and Banti's disease, *Practitioner*, 1914, *XCII*, 470.
- 16 WARTHIN, A. S. Relation of thrombophlebitis of the portal and splenic veins to splenic anemia and Banti's disease, *International Clin.*, 1910, *IV*, 189-226.

ALLERGIC CORYZA AT MENSTRUATION FROM OVARIAN HORMONE¹

By FRANK A. RIEBEL, M D, *Columbus, Ohio*

THE symptoms which may be associated with menstruation are numerous and varied. The majority of them are plainly the result of the cyclic functional and structural changes in the genital tract, but occasionally the history suggests an allergic basis for the phenomena. Such a case is described here.

CASE REPORT

E. S., married, a white female aged 29, complained of frequent attacks of coryza, these began regularly the day before or the first day of her menstrual period. The initial symptoms were malaise and frontal headache, and these were followed by sneezing, nasal obstruction, chills, fever of about 101°, and prostration. Within 24 hours of the onset the patient had been confined to her bed during every menstrual period for one year. The disability would continue for about two days, to be followed by symptoms diminishing in intensity for three or four more days. The thickness of the nasal discharge was varied and occasionally was burning to the nostrils. There was no lachrymation. Ephedrine gave moderate relief.

For about the same length of time a tachycardia averaging 140 beats per minute had been present for brief periods. This was most marked during or following the coryzal attacks, but also occurred at other times. Diligent search had been made for an etiological agent here, but without results. Roentgen-rays of the teeth, sinuses and chest were all negative, the heart was normal in size, sounds and contour. The Kahn test was negative and the basal metabolic rate normal.

Menstrual History The periods began at 13 years and were regular at once, being of the 28/5 day type. Two children have been borne. For the last four periods of the present illness the intervals had changed to a 24/2 day type.

Family and Past History The maternal grandfather had had "miner's asthma." There were no other hereditary factors apparent. The patient herself has noticed a sensitivity to absorbent cotton for years, the latter producing symptoms of coryza.

In the belief that the coryza might be allergic, certain cutaneous and therapeutic tests were made as follows:

On November 10, 1933, which was seven days following the first day of the last menstrual period, a cutaneous scratch test was made using an aqueous solution of crystalline folliculin as a test reagent and with an alkaline solution for a control. A faintly positive reaction was elicited.

On November 13 and 16, the test was repeated and faintly positive reactions were again elicited. On November 19 and 22, tests were negative.

The patient was menstruating and was bedfast on November 27. On December 2, 7, 10 and 12, cutaneous tests were negative. December 3 to 6 of this period, the patient was suffering from acute rhinitis, apparently not related to the condition being discussed.

On December 14, one c.c. of aqueous solution of folliculin (theelin) was injected subcutaneously. Six hours later malaise and chills appeared, to be followed by a coryza similar to, but not quite so intense as that of the menstrual period. This remained until December 18. On December 20, the patient began to menstruate but had no evidences of coryza. One c.c. of folliculin was readministered, this was enough to elicit mild symptoms of coryza. The menstruation ceased on December 22. On December 25, folliculin was again injected and was promptly followed by a coryza which lasted for two days.

* Received for publication May 21, 1935

On January 8, one c c of folliculin was sprayed on the nasal mucosa. This gave rise to a coryza within 30 minutes, which lasted through January 9.

On January 10, the patient being free from symptoms, folliculin was again administered intranasally. Symptoms reappeared promptly to last through January 11 and 12. On January 15, folliculin was administered subcutaneously, this brought forth a very slight reaction. From January 16, to 19, the patient was menstruating and was free from symptoms for the first time in over a year.

From January 25 to March 31 exclusive, 13 doses of folliculin were administered by means of vaginal suppositories at from three to five day intervals. On two of these occasions mild symptoms of malaise appeared, on the other days there was no reaction whatever.

From February 10 to 14 and again from March 14 to 18 normal menstruation took place.

Our evidence that the coryza is allergic may be summarized thus:

- (1) A positive cutaneous reaction (though not marked) was secured.
- (2) The allergic manifestation was artificially reproduced at will by the administration of folliculin.
- (3) Tolerance to the agent was secured by repeated administrations which resulted in the total relief of symptoms.

It would seem, therefore, that in this case folliculin has been proved to be an allergic agent, giving rise to a coryza at the menstrual period, by some mechanism which we are not prepared to explain.

EDITORIALS

EMOTIONS AND BODILY CHANGES

THE appearance just recently of an extensive bibliography¹ upon the subject of the relation of the emotions to bodily changes should help to stimulate further thought among internists upon the status of this problem in the practice of medicine. The consultant internist especially will be interested since a large fraction of consultant practice is made up of those cases which present the problem of assessing the proportionate parts played by psychic and somatic factors in the development of the patient's disability. Both factors we have come to believe are involved in most cases but in some the dominant rôle is played by organic disease and in some by the psychic disturbance. The nature of these complex interrelationships is still all too obscure. A better understanding of their scope, a deeper insight into their *modus operandi* are urgently needed to bring this lagging wing in line with the front of medical advance.

In the field of diagnosis the question presents itself to the practising physician almost daily in this form:

How may disturbances in bodily function not accompanied by known structural changes in the tissues, but associated with important disturbances in the psyche, be differentiated from disturbances in bodily function which are associated with important structural changes and are accompanied by relatively minor disturbances in the psyche?

The usual method of procedure is to obtain a careful record of the symptoms, from the patient's own account of them and by observation of the objective phenomena which are detectable during their occurrence, and, further, to determine if possible, by physical examination and by special tests the nature of the functional abnormalities and the presence or absence of structural changes. These methods are carried out with varying degrees of thoroughness and skill according to the ability of the physician, the intelligence of the patient, and the availability of the special tests involved.

The study of the psychical component of the illness is of course of equal importance in such a differentiation. Skill in this study is certainly rarer than is skill in the study of objective bodily phenomena. There is current among psychiatrists an impression that the average physician totally ignores the importance of such a study. This is certainly an unfortunate error dependent in part upon the isolation of the average psychiatrist from the field of general practice and in part upon the fact that he sees very much more of the failures of the practitioner than of his successes. In part too it may be due to the fact that methods of study vary so widely in this field and that the busy practitioner's "sizing up" of the patient's situation and of his

¹ DUNBAR, F. H. *Emotions and Bodily Changes. A Survey of Literature on Psychosomatic Interrelationships 1910-1933.* Published for The Josiah Macy Jr. Foundation, Columbia University Press, New York, 1935.

psychic reactions to it, seems too crude to the psychiatrist to be given any credit at all. Yet to those who are in closer touch with the realities of medical practice it will not seem an exaggeration to state that those physicians who attain success in general practice are almost universally possessed of a keen discrimination in differentiating the psychic disturbances which are dominant in a disease picture of functional type from those which are merely associated with important organic disease. Nor will it seem exaggerated to say that lasting success in general practice is largely dependent upon efficient discrimination of this type.

The method described above as being that in general use for solving the question as to the differentiation of these cases in which psychic and somatic disturbances coexist is dependent for its efficiency upon the existence of detectable differentiae between functional somatic disturbances due to organic disease and those not due to organic disease, and likewise between psychic disturbances whose causes lie in the relations of the psyche to the external environment in the broadest sense, and those which have arisen in response to somatic dysfunctions.

It must be acknowledged that while the accuracy of diagnosis of non-organic functional disturbances is well supported as a rule by the observed later course of these patients, this is less uniformly true of our diagnosis of organic disease. We still urgently need new methods of differentiation. Too many gross errors are still made in both directions, too many cases treated with drugs or by surgical procedures for conditions requiring primarily psychiatric care, and too many organic conditions passing undetected under the guise of neuroses.

The question arises whether the advance will be made by further perfection of the methods of somatic diagnosis or by progress in the field of psychiatric study.

Many have stated that from the point of view of immediate improvement in the existing level of medical practice in this respect the most urgent requisite is that more psychiatric training should be given to medical students since the average physician is undoubtedly weaker on this side than in his knowledge of the structural aspect of disease. This is no doubt true and the present widespread tendency to increase the time devoted to psychiatry in the curriculum will be justified.

Ultimately, however, it is questionable whether psychiatry, at least in any of its present forms, will furnish the practitioner with a further advance in method of study of such problems beyond what is now available. At least one may say that Dunbar's compilation of the writings of psychiatric authors in the last twenty-three years on psychosomatic interrelationships contains very little which promises further help. It appears to be a surprisingly uncritical literature, devoted in large part to semi-philosophical speculations, inclined too often to deal with assumptions as if they were proved facts and betraying in its fertility as to terminology an attempted compensation for its sterility as to tangible accomplishment. We have

learned more in these last twenty years of the nature of the relationship between mind and body from a few physiologists such as Pavlov and Cannon than from all the psychiatrists. It is not to be wondered at. Emotions *per se* are immeasurable and imponderable, but their repercussions upon bodily behavior lend themselves to quantitation. It seems probable that as the mechanisms which bring about these bodily changes become better known we shall find in them distinctive characteristics of a measurable nature which will differentiate them from those mechanisms set at play through the mechanical, toxic or metabolic effects of inflammatory, neoplastic, or degenerative diseases.

DINITROPHENOL AND CATARACT

In our next issue there will be published a brief report on eight cases of rapidly developing cataract appearing in relatively young women during or shortly after treatment with dinitrophenol for obesity. With the consent of Dr. W. W. Boardman, the author, this advance notice is given to our readers of this new danger associated with the use of this drug. Its employment in the Stanford Clinic has been discontinued.

•

REVIEWS

The Principles and Practice of Neurology By ALEXANDER CANNON and E D TRANCHELL HAYES \ + 333 pages, with 114 illustrations William Heinemann, Ltd, London, England 1934 Price 25 s

In the preface the authors state that "the purpose of this book is to present to the student and practitioner of neurology the essentials in the clinical examination, diagnosis, and treatment of nervous diseases" On the first score they have succeeded admirably The first 55 pages are devoted to the clinical examination The authors chose wisely in having Professor G H Monrad-Krohn present this important section It is a careful, concise presentation on the methods of examination and is actually an abridged presentation of this author's excellent textbook, "Clinical Examination of the Nervous System" Any student mastering these chapters should be able to do a careful and intelligent examination The method presented is essentially the one used and taught by the British School of neurologists Professor Monrad-Krohn, although a Norwegian, has studied extensively in England This chapter includes a few pages on history taking, discussion of cranial nerves, motor system, sensory system, and reflexes The appendix to these chapters includes the electrical examination and an excellent discourse on aphasia

Part II of the text presents the major neurological disorders of the nervous system The plan of these chapters is very disturbing and will undoubtedly be grossly confusing to students Obviously it is a very difficult task to present the subject of neurology in a single volume, consequently some orderly and logical grouping of diseases is the first requirement This seems to be entirely lacking Chapters 2 and 3, for instance, cover thirteen entities, ranging from exophthalmic goiter to the neuralgias

Chapter 4 discusses the hereditary and familial nervous diseases This grouping has the advantage of impressing the student with the magnitude of this great group of diseases On the other hand, it would seem difficult for the beginner because of the lack of anatomical and pathological grouping Diseases such as the myopathies have little in common with Wilson's disease, for instance, except the common factor of being hereditary affections

Under the heading of "Epidemic Diseases of the Central Nervous System" in Chapters 5 and 6, both epidemic and non-epidemic subjects are discussed Further, it is difficult to see why cerebellar palsies in children and hydrocephalus should be classified in this section Many other such odd groupings will be found throughout the book

In the discussion of each disease, a uniform plan is adhered to definition, etiology, signs and symptoms, differential diagnosis prognosis and course, and treatment Many of these disease pictures are clearly drawn, notably multiple sclerosis Very little emphasis has been placed on treatment The treatment of subacute combined degeneration seems very inadequate In the treatment of Meniere's disease, no mention is made of surgical section of the eighth nerve

The book as a whole does not seem to be an ideal student's text, and is not detailed enough for a reference work

J G A, JR

Disease, Gadfly of the Mind By WILLIAM ALLEN PUSEY, A M, M D, L L D 20 pages, 17.5 x 24.5 cm H K Lewis and Co, Ltd, London 1934

"That which has led us to where we are is not the beckoning of a plump and genial angel but shrewd prods from the sharp stick of necessity" The author's thesis in this the Prosser-White Oration before the St Johns Hospital Dermatological Society, is that diseases as a goad to thought have been among the most active

agents in the making of the mind and that among diseases few have been so powerful in this respect as diseases of the skin. The development historically of this thesis constitutes the body of this most interesting address

M C P

The Care of the Aged, the Dying, and the Dead By ALFRED WORCESTER, M D, Sc D
vi + 77 pages, 13 × 18 cm Charles C Thomas, Springfield, Illinois 1935
Price, \$1 00

Lectures from which the student and the practitioner alike may derive a broader and finer conception of the physician's rôle in the care of those whom he cannot cure

The Harvey Lectures, 1933-1934, Series XXIX By R E DYER, W MANSFIELD CLARK, ROSS G HARRISON, E A DOISY, EVARTS A GRAHAM, GEORGE L STRELTER, THOMAS M RIVERS, and DETLEV W BRONK 262 pages, 14 × 20 5 cm Williams and Wilkins Company, Baltimore 1935 Price, \$4 00

The Harvey Lectures are seldom light summer reading for the tired practitioner. Indeed the alert internist will find many of them outside the scope of his interests if not of his comprehension. In the present volume, however, there are a number of papers of the greatest value to all students of medicine. The lecture by R E Dyer on "Typhus and Rocky Mountain Spotted Fever in the United States" is an authoritative statement of the broad outlines of this important health problem. Most stimulating also are the lectures by Rivers on the filterable viruses, by Graham on "Clinical Application of Some Recent Knowledge of the Biliary Tract," and by Doisy on "The Estrogenic Substances." The lecture by Bronk on "The Nervous Mechanism of Cardiovascular Control" is a beautifully clear exposition of experimental investigations of circulatory regulating mechanisms which have only recently been discovered. This lecture in itself would make the volume a worthwhile addition to any internist's library

M C P

Treatment by Diet By CLIFFORD J BARBORKA, B S, M S, D Sc, F A C P 615 pages, 15 × 23 cm J B Lippincott Co, Philadelphia 1934 Price, \$5 00

This is a well-organized book on diet. The chapter on The Application of Dietotherapy contains useful photographs illustrating comparative servings of typical foods. There is little discussion of the basic principles of nutrition or of the origins and uses of individual foodstuffs, the major portion of the work being a description of the diets useful in individual diseases. The book is filled with many sample diets. The author makes a useful distinction between diseases in which diet is of paramount importance and conditions in which it is of varying importance. An appendix contains the usual food tables and a few recipes. There is a good bibliography and adequate index.

G A H

Simplified Diabetic Management By J T BEARDWOOD, JR, and HERBERT T KLLLY 211 pages, 19 5 × 13 cm Second Edition J B Lippincott Co, Philadelphia 1934

The unusual feature of this diabetic manual is the "Unit Method" developed by the authors for calculating the diabetic diet, which seems to be an adaptation of the "Line-ration scheme" introduced by Lawrence and widely employed in Great Britain. It is used in conjunction with a somewhat elaborate "Diet Prescription Chart" which automatically gives the proper diet formula, according to the authors' conception, as well as the number of food 'units' required to prepare it.

The book contains the usual subject matter to be found in diabetic manuals of this type, and in general the material is presented clearly. It is interesting that the modern conception of shock in diabetic coma and the measures required for treating it, a matter which most students now believe is quite as important as the factor of acidosis, receive almost no consideration at all. Electrocardiograms are advised in all cases in which surgery is contemplated so that "cases of early coronary disease may be discovered." The book contains tables of food values and a list of recipes.

G A H



JAMES ALEXANDER MILLER, A B, A M, M D, S c D, F A C P
NEW YORK CITY

PRESIDENT OF THE AMERICAN COLLEGE OF PHYSICIANS 1935-1936

JAMES ALEXANDER MILLER, A B , A M , M D., Sc D ,
F A C P , NEW YORK CITY

PRESIDENT OF THE AMERICAN COLLEGE OF PHYSICIANS
1935-1936

Born, Roselle, N J , March 27, 1874, graduated from Princeton University, A B , 1893, A M , same, 1894, College of Physicians and Surgeons of Columbia University, M D , 1899, Columbia University, Sc D , 1930

Dr Miller interned in the Presbyterian Hospital, New York City, 1899-1901 He has been connected with Bellevue Hospital since 1903 He began as Assistant Visiting Physician in General Medicine, First Division, later being promoted to Visiting Physician, holding this appointment for ten years, whereupon he became Visiting Physician in charge of the Tuberculosis Service, resigning his former position in General Medicine This latter position he has held continuously for more than twenty years

For the past fifteen years, Dr Miller has been Professor of Clinical Medicine in Columbia University College of Physicians and Surgeons He is Consultant to the New York Postgraduate Medical School and Hospital, to the Methodist Episcopal Hospital, to the Trudeau Sanatorium and to Sprain Ridge He is also Consultant in Tuberculosis to the Presbyterian Hospital

Dr Miller has been President of the New York Tuberculosis Association, the National Tuberculosis Association and the American Clinical and Climatological Association He is a Trustee of the New York Academy of Medicine, and has been Chairman of its Public Health Committee for the past fifteen years He is President of the Board of Trustees of the Trudeau Sanatorium During the World War, he was Medical Director of the Rockefeller Tuberculosis Commission in France, and was Major of the American Red Cross He received the decoration of Chevalier Legion d'Honneur He is a member of the Central Council Charity Organization Society, a member of the Board of Managers of the Association for Improving the Condition of the Poor and a member of the Technical Board of the Milbank Memorial Fund In addition, Dr Miller is a member of the New York Medical and Surgical Society, the New York Practitioners Society, the American Association of Thoracic Surgery, the American Clinical and Climatological Association, the New York Academy of Medicine, the American Medical Association and the Association of American Physicians He is also a member of the University, Century and Deepdale Clubs

Dr Miller is the author of a large number of scientific articles dealing primarily with diseases of the chest, especially tuberculosis He contributed the chapter on "Chronic Pulmonary Disease" in Musser's *Internal Medicine*, published by Lea and Febiger, he contributed the chapter on "Pulmonary Tuberculosis" in Nelson's *System of Medicine*

Dr Miller became a Fellow of the American College of Physicians in 1926, and has served on its Board of Regents since 1928 He has been particularly active on its Committee on Public Relations and its Committee on Finance He enters upon his term as President with an intimate knowledge of the College's problems, and with a deep appreciation of the respon-



ERNEST B. BRADLEY, A.B., M.D., F.A.C.P.
LEXINGTON, KY

PRESIDENT-ELECT OF THE AMERICAN COLLEGE OF PHYSICIANS 1935-1936

ERNEST B BRADLEY, A B , M D , F A C P
LEXINGTON, KY

PRESIDENT-ELECT OF THE AMERICAN COLLEGE OF
PHYSICIANS 1935-1936

Born, Lexington, Ky , May 16, 1877, educated in the Lexington Public Schools, Transylvania University, A B , 1895, Postgraduate study in Chemistry, University of Kentucky, 1895-1896, Instructor in the Fayette County (Ky) Schools and the Lexington City School System for five years, University of Michigan Medical School, M D , 1904, Intern, New York City Hospital, 1904-1905, postgraduate research work in New York City, 1906 Dr Bradley has practiced medicine in Lexington, Ky , since 1907 He has held the following appointments City Bacteriologist, Lexington, 1908-1925, Part-time Health Officer, Fayette County (Ky), 1909-1924, Chairman, Fayette County Board of Health, 1924 to date, Member, Lexington City Board of Health, 1932 to date, Visiting Physician, St Joseph's Hospital and Good Samaritan Hospital, 1907 and 1909 to date, respectively, Member, Medical Advisory Board, Julius Marks Sanatorium (for Tuberculosis), Lexington, 1921 to date

Dr Bradley is a member and ex-President of the Fayette County Medical Society, an ex-President of the Kentucky Midland Medical Society, a member of Kappa Alpha and Nu Sigma Nu fraternities, member of the Kentucky State Medical Association, Fellow of the American Medical Association, member, ex-Vice Chairman, ex-Secretary and ex-Chairman of the Section on Medicine of the Southern Medical Association and member of the American Clinical and Climatological Association During the World War, he was Major in the Medical Corps of the U S Army, acting as Chief of Medical Service of X-section, Camp Jackson, Columbia, S C , and for a time was Chief of Medical Service at the Henry Ford Hospital, Detroit, Mich He has been a member of the Lexington Clinic since its organization in 1920

Dr Bradley became a Fellow of the American College of Physicians in 1919 He served as the Governor for the State of Kentucky since 1926, and as Chairman of the Board of Governors since the death of the former Chairman, Dr W Blair Stewart, of Atlantic City, in 1933 For a number of years, Dr Bradley has been a member of the Committee on Credentials, where he has given unstintingly of his ability and time

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Dr Edward Schons (Fellow), St Paul, Minn—1 reprint,
Dr Arthur A Shawkey (Fellow), Charleston, W Va—1 reprint,
Major James S Simmons (Fellow), Ancon, C Z—1 reprint

Dr J K Pepper (Fellow), Winston Salem, N C, was elected first Vice-President, Dr L B McBrayer (Fellow), Southern Pines, N C, was reelected Secretary-Treasurer, Dr Wingate M Johnson (Fellow), Winston Salem, N C, was elected a member of the House of Delegates to the American Medical Association for two years, and Dr C C Carpenter (Fellow), Professor of Pathology, Wake Forest College, was appointed Chairman of the Committee on Cancer for the ensuing year

Dr Allen H Bunce (Fellow), Atlanta, Ga, has retired as Secretary-Treasurer of the Medical Association of Georgia after 15 years

Dr Paul H Ringer (Fellow), Asheville, N C, was inducted as President of the Medical Society of the State of North Carolina at their meeting in Pinehurst in May
Dr P P McCam (Fellow), Sanatorium, N C, was the retiring President

Dr Verne S Caviness (Fellow), Raleigh, N C, and Dr J Buren Sidbury (Fellow), Wilmington, N C, were guest speakers at the spring meeting of the Third District Medical Society of North Carolina, held at Jacksonville, N C, May 31

Dr Bernard L Wyatt (Fellow), Tucson, Ariz, addressed the annual meeting of the Nebraska State Medical Association at Omaha, May 14 to 16, on "The Treatment of Chronic Arthritis" and "The Economic Aspects of Chronic Arthritis"

Dr Frederick T Lord (Fellow), since 1930 Clinical Professor of Medicine at Harvard University Medical School, has retired from the faculty as Professor Emeritus

The Fifth Annual Fever Conference for physicians and others interested in the production of fever by physical methods and its use in the treatment of disease was held at Dayton, Ohio, May 2 to 3. Among those who addressed the meeting were Dr Philip S Hench (Fellow), Rochester, Minn, "Results of Fever Therapy for Gonorrheal Arthritis, Chronic Infectious (Atrophic) Arthritis and Other Forms of 'Rheumatism'", Dr Walter M Simpson (Fellow), Dayton, Ohio, "Report of Fever Therapy Research at Miami Valley Hospital", Dr Frank H Krusen (Associate), Philadelphia, Pa, "Studies of Blood Picture Before and After Fever Therapy", Dr Ralph H Kulins (Associate), Chicago, "Present Status of Fever Therapy for Dementia Paralytica in the State Hospitals of Illinois"

Dr William A White (Fellow), Professor of Nervous and Mental Diseases at George Washington University School of Medicine, and Superintendent of St Elizabeth's Hospital, Washington, D C, delivered a series of three lectures known as the Thomas William Salmon Memorial Lectures at the New York Academy of Medicine during April

Dr David A Tucker, Jr (Fellow), Associate Clinical Professor of Contagious Diseases at the University of Cincinnati College of Medicine, has been appointed Professor of the History of Medicine in the same institution

Dr Philip F Barbour (Fellow) and Dr Thomas Cook Smith (Fellow) were among those on the teaching staff of the Children's Free Hospital, Louisville, Ky, where a 10 weeks' course in Pediatrics has been conducted under the auspices of the American Academy of Pediatrics The course extended from April 24 to June 26

Under the Presidency of Dr Samuel E Thompson (Fellow), Kerrville, Texas, the 69th Annual Meeting of the Texas State Medical Association was held in Dallas, May 14 to 16 Among guest speakers were the following Dr Joseph L Miller (Fellow), Chicago, "Recent Advances in Our Knowledge of the Thyroid Gland", Dr Horton R Casparis (Fellow), Nashville, Tenn, "Allergy in Children", Dr Arthur U Desjardins (Fellow), Rochester, Minn, "Radiotherapy for Acute and Chronic Inflammatory Conditions", and Dr Albert C Broders (Fellow), Rochester, Minn, "Cancer as We Comprehend It"

Dr Charles W Burr (Fellow), Professor Emeritus of Nervous and Mental Diseases, University of Pennsylvania School of Medicine, was the recipient of the twelfth annual Strittmatter Award of the Philadelphia County Medical Society recently A bronze tablet bearing the names of three benefactors of the County Society was unveiled The names included were Dr Isidor P Strittmatter, donor of the award, Dr James M Anders (Master), founder of the Library, and the late Dr Lawrence Webster Fox, a contributor to the support of this society

Under the Presidency of Dr Henry Kennon Dunham (Fellow), Cincinnati, Ohio, the National Tuberculosis Association held its thirty-first annual meeting at Saranac Lake, N Y, June 24 to 27 Many Fellows of the College took part in the program

Under the Presidency of Dr Ernest E Irons (Fellow), Chicago, the second annual meeting and the fourth conference of the American Association for the Study and Control of Rheumatic Diseases was held at Atlantic City, June 10 Half the day was devoted to consideration of chronic arthritis and the other half to rheumatic fever

Dr Charles F Craig (Fellow), New Orleans, La, has been elected President of the American Academy of Tropical Medicine for 1935 to 1936

Dr Earl B McKinley (Fellow), Washington, D C, was reelected Secretary

Dr Louis H Fligman (Fellow), Helena, Mont, has been appointed Vice-President of the Montana State Board of Health

Dr T Grier Miller (Fellow), Dr Richard A Kein (Fellow) and Dr Charles C Wolferth (Fellow), formerly Assistant Professors, have been advanced to fill three new Clinical Professorships established at the University of Pennsylvania School of Medicine

Dr Truman G Schnabel (Fellow) has been advanced from Assistant Professor of Medicine to an Associate Professorship

A portrait of Dr Martha Tracy (Fellow), Dean of the Woman's Medical College of Pennsylvania, has been presented to the College on its eighty-fifth anniversary and the twenty-fifth anniversary of Dr Tracy's connection with the College. The presentation was made by Dr Ellen C Potter (Fellow), of Trenton, N J. Dr Tracy was personally presented with an automobile by the trustees, faculty, students and friends of the College

Dr Lewellys F Barker (Fellow), Professor Emeritus of Medicine, Johns Hopkins University School of Medicine, delivered the Abner Wellborn Calhoun Lecture on the "Treatment by the General Practitioner of the More Common Diseases of the Nervous System" in connection with the annual meeting of the Medical Association of Georgia at Atlanta, May 7 to 10

Among Fellows of the College who have delivered lectures during the months of May and June in connection with the Ballin Memorial Lectures at the North End Community Clinic, Detroit, were Dr Solomon Strouse (Fellow), Chicago, "Obesity and Malnutrition, Their Causes and Management", Dr Robert C Moehlig (Fellow), Detroit, "Pituitary Disturbances", Dr Hugo A Freund (Fellow), Detroit, "Thyroid Disturbances", Dr I M Rabinowitch (Fellow), Montreal, "Newer Views in the Diagnosis and Treatment of Diabetes Mellitus"

Dr Marcus W Newcomb (Fellow), Browns Mills, N J, was inducted as President of the Medical Society of New Jersey at its one hundred and sixty-ninth annual meeting at Atlantic City, recently

OBITUARIES

DR HENRY AARON NORDEN

Dr Henry Aaron Norden (Fellow), of Fort Wayne, Ind, and Chicago, Ill, died May 1, 1935, of hemiplegia, hypertension and arteriosclerosis

Dr Norden was born in New York City in 1867, but later removed to Chicago, where he received his preliminary education under private tutors and his medical training at the Rush Medical College, from which he graduated in 1889. Although he had been retired from active practice of medicine for some time, he was formerly attending physician to the Cook County Hos-

pital, Chicago, Superintendent of the Winfield Tuberculosis Sanatorium, Chicago, Consulting Physician to the Chicago Municipal Sanatorium and Professor of Chest Diseases and Junior Dean of Loyola University School of Medicine. At one time he was the School Health Officer of the City of Chicago. He had been a Fellow of the American College of Physicians since 1919.

DR. JAMES HUNT ROYSTER

Dr. James Hunt Royster (Fellow), born at Townsville, North Carolina, June 29, 1892, died at his home at Richmond, Virginia, March 22, 1935. He was the son of the late Dr. Thomas S. Royster and Sally Alston Royster. His early education was received in the private schools in his county and he was graduated from the Waverly, North Carolina, High School in 1909. He entered the University of North Carolina, from which he was graduated with the degrees of Bachelor of Arts and Master of Arts in 1913. He entered the Medical College of Virginia that same year, where he pursued his studies for two years, transferring to the Jefferson Medical College in Philadelphia, receiving his medical degree in 1917. He immediately was commissioned as Lieutenant—Junior grade, in the United States Navy, in which service he remained until 1921. He spent practically the entire duration of the war in foreign waters. At the expiration of the war he returned to the Brooklyn Naval Hospital where he remained on duty until his discharge from the service in 1921. Shortly after his return from overseas, he was promoted to the rank of Lieutenant—Senior grade, in the United States Navy.

Dr. Royster had always been interested in psychiatry, and made a special study of it during his service in the Navy. Thus, in 1921 he was appointed associate chief of staff at the Westbrook Sanatorium in Richmond, Virginia, which institution he served until his death.

He was a member of the Governor's Advisory Board of Mental Hygiene. He belonged to the Richmond Academy of Medicine, the Medical Society of Virginia, the Southern Medical Association and the American Medical Association. In 1930 he was made a Fellow of the American College of Physicians. He was a member of the Pi Kappa Alpha Fraternity and the Phi Chi Medical Fraternity. At the time of his death he was Vice-Chairman of the section of Neurology and Psychiatry of the Southern Medical Association.

He is survived by his wife, Mrs. Louise Moss Royster of Richmond, Virginia, his brother, Dr. Thomas S. Royster of Henderson, North Carolina, and two sisters, Mrs. William B. Tarrey of Townsville, North Carolina, and Mrs. Salley Royster Vaughan of Wilson Mills, North Carolina.

Dr. Royster's large circle of friends will mourn his death. He was a loyal friend and greatly beloved by all those with whom he came in contact.

FINLEY GAYLE, F. A. C. P.

DR WALTER FORD HENDERSON

Dr Walter Ford Henderson (Fellow), born January 3, 1892, near Shreveport, La, died at New Orleans, April 18, 1935

Dr Henderson was graduated from Millsaps College, Jackson, Miss, in 1912. He received his medical degree from Vanderbilt University Medical School in 1916

From August 1917, until June 1918, he served as Lieutenant in the Medical Corps of the United States Army at Fort Riley, Kansas, at which time he was honorably discharged on account of physical disability

Following this he practiced medicine at Shreveport, La, and at DeRidder, La. In 1921 he began the intensive study of Roentgenology, pursuing postgraduate work at Tulane University, Johns Hopkins Hospital and the University of Michigan. He later became Director of the Roentgen-Ray Department of the Baptist Hospital in Jackson, Miss. In 1925 he became Director of the Roentgen-Ray Department of Toulo Infirmary in New Orleans. In December 1932, he resigned from the Touro Infirmary to go to the Mayo Clinic for an operation for gastric ulcer

After recovery he returned to Jackson, Miss, May 1933, again to become the Director of the Roentgen-Ray Department at the Baptist Hospital, which position he held until his death

Dr Henderson was a member of the Cential Medical Society, Orleans Parish Medical Association, New Orleans Gastro-Enterological Society, Mississippi State Medical Society, Louisiana State Medical Association, Southern Medical Association, American Medical Association and the Radiological Society of North America. He was also a member of the Phi Rho Sigma Medical Fraternity and the Kappa Alpha Social Fraternity. He was President of the Mississippi Art Association and a member of the Executive Committee of the New Orleans Art Association. He became a Fellow of The American College of Physicians in 1928

EXCERPTS FROM MINUTES OF THE MEETINGS OF THE BOARD OF REGENTS

PHILADELPHIA, PA

April 28, 1935

The first meeting of the Board of Regents, in connection with the Nineteenth Annual Clinical Session of the American College of Physicians, was held at Philadelphia, April 28, 1935, presided over by the President, Dr Jonathan C Meakins, with the following members of the Board present Dr Jonathan C Meakins, Dr James Alex Miller, Dr Randolph Lyons, Dr James F Churchill, Dr William D Stroud, Dr David P Barr, Dr Arthur R Elliott, Dr James B Herrick, Dr Clement R Jones, Dr S Marx White, Dr Walter L Bierring, Dr John H Musser, Dr O H Perry Pepper, Dr Francis M Pottenger, Dr Luther F Warren, Dr Roger I Lec, Dr Sydney R Miller, Dr George Morris Piersol, Dr G Gill Richards, Dr Ernest B Bradley, and the Executive Secretary, Mr E R Loveland

After reading of the Minutes of the previous meeting of the Board, and approval thereof, the Executive Secretary presented the communications

Dr O H Perry Pepper presented a recommendation that the College omit the word "Clinical" in the name of the annual meeting, giving as his reasons, first, that this is the only meeting the College holds, and, second, that it is not wholly clinical, and, third, that the present title would indicate a program of clinical sessions only

On motion by Dr Pottenger, seconded by Dr Herrick, and regularly carried, it was RESOLVED, that in the future the annual meeting shall be known as "Annual Session of the American College of Physicians"

The following resignations, acted upon separately, by resolution, were accepted

Fellow

Dr Arthur W Grace, New York, N Y

Associates

Dr Bernard T Brown, Cazenovia, N Y

Dr John R Claypool, Mt Vernon Ohio

Dr Albert J Michels, East Liverpool, Ohio

Dr Daniel B Street, Jersey City, N J

Ten cases involving fees and dues of Fellows and Associates were presented and individually acted upon

On motion by Dr Ernest B Bradley, seconded by Dr S Marx White, and regularly carried, it was

RESOLVED, that in order to expedite the handling of special cases pertaining to resignations, fees and dues, in the future, the Executive Secretary shall present all such communications to one of the standing committees, to be designated by the President, and that that Committee shall bring in its recommendations to the Board of Regents

Dr Harry Brandman (Associate), Whiting, Indiana, was discontinued from the Roster for failure to take up election in accordance with provisions of the By-Laws

In the absence of the Secretary-General, Dr William Gerry Morgan, because of illness, President Meakins presented his report, including, among other matters, the report of the death of 18 Fellows and nine Associates since the 1934 Session Deaths not previously reported to the Board were

Fellows

Dr E Rodney Fiske, New York, N Y

Dr Edgar Moore Green, Easton, Pa

Dr J R Morrison, Louisville, Ky

Dr James Hunt Royster, Richmond, Va

Dr Harry S Wagner, Pocasset, Mass

December 19, 1934

March 9, 1935

January 8, 1935

March 22, 1935

February 8, 1935

Associates

Dr William S Hannah, Montgomery, Ala

Dr H D Lawhead, Woodland, Calif

Dr Kenneth G Mowat, Buffalo, N Y

Dr James E Campbell Taylor, Columbus, Ohio

Dr Stephen L Taylor, Sherrill, N Y

March 22, 1935

November 29, 1934

January 13, 1935

December 13, 1934

January 29, 1935

President Meakins presented a report on Life Membership, indicating that the list of Life Members had increased considerably since the 1934 Session, and that there had been a larger number added to the Life Membership Roster during the past year than during any previous year. There are at this time 49 Life Members, of which the following 11 are new

Dr Henry I Klopp, Allentown, Pa
 Dr Ralph O Clock, New York, N Y
 Dr Charles F Morsman, Hot Springs, S D
 Dr Lawrason Brown, Saranac Lake, N Y
 Dr Grant O Favorite, Philadelphia, Pa
 Dr James Alex Miller, New York, N Y
 Dr Edward C Klem, Jr, Newark, N J
 Dr Joseph M King, Los Angeles, Calif
 Dr William J Stapleton, Jr, Detroit, Mich
 Dr George Edwin Baxter, Chicago, Ill
 Dr Clifford E Henry, Minneapolis, Minn

A general report on the Philadelphia Session was made by President Meakins and the Executive Secretary

Dr George Morris Piersol, Chairman of the Committee on Credentials, reported that his Committee had met at the College Headquarters in Philadelphia on March 30, 1935, and had examined the credentials of 68 candidates for Fellowship and 115 candidates for Associateship. At another meeting of the Committee on April 28, the Committee had examined the credentials of 35 candidates for Fellowship and 70 candidates for Associateship.

Upon motion by Dr Piersol, on behalf of the Committee on Credentials, seconded by Dr G Gill Richards, and regularly carried, it was

RESOLVED, that the following candidates be and herewith are elected to Fellowship in the American College of Physicians

(There were 82 candidates whose names already have appeared in the College News Notes Section of the May Issue of this journal)

On motion by Dr Piersol, on behalf of the Committee on Credentials, seconded by Dr O H Perry Pepper, and regularly carried, it was

RESOLVED, that the following candidates be and herewith are elected to Associateship in the American College of Physicians

(There were 151 candidates whose names already have appeared in the College News Notes Section of the May Issue of this journal)

On motion by Dr James Alex Miller, seconded by Dr Musser, and regularly carried, it was

RESOLVED, that the Committee on Credentials adopt a feasible plan in the future for presenting to the Board of Regents in advance a list of the recommendations, both for Fellowship and Associateship, so that the reading of the list would be unnecessary, and individual members of the Board would be ready to take immediate action without unnecessary discussion and consequent delay.

Dr George Morris Piersol further reported that the Committee on Credentials, through communication with the Surgeon Generals of the U S Army and U S Navy, had established the following criteria, which are considered very satisfactory to the College, for the selection of men for Associateship and Fellowship.

Officers of the Medical Corps of the U S Army and of the U S Navy shall be nominated in each instance by the Surgeon General of the Service concerned, as is the present practice, a method that assists in maintaining the high morale and efficiency of the two medical Services. In making nominations, the Surgeon Generals are in entire accord with the importance of presenting only the names of such men as will be a credit to the American College of Physicians, and who, by the character of their professional work and their experience in the medical field, fully meet the requirements for Associateship and Fellowship.

"Eligibility for Associateship in the American College of Physicians shall be limited to Officers who have had a minimum of five years of military or naval service, with ample clinical experience in internal medicine, laboratory work, or roentgenology, and eligibility for Fellowship shall be limited to Officers who have had a minimum of ten years of military or naval service, with broad experience under qualified supervision in the field of internal medicine, laboratory work, or roentgenology.

"However, there are a few Senior Officers of extensive experience in internal medicine in both Services who may be nominated for initial appointment as Fellows, without passing through the grade of Associate, provided the Surgeon General of the Service concerned fully

sets forth their special qualifications at the time they are nominated. The number available for such exceptional consideration is limited, and their nomination will be presented during the current calendar year."

April 30, 1935

The second meeting of the Board of Regents of the American College of Physicians was held in the Philadelphia Municipal Auditorium, Tuesday, April 30, with President Jonathan C. Meakins presiding, the Executive Secretary, Mr. E. R. Loveland, acting as Secretary, and with the following present: Dr. Jonathan C. Meakins, Dr. James Alex. Miller, Dr. James H. Means, Dr. Randolph Lyons, Dr. James F. Churchill, Dr. William D. Stroud, Dr. David P. Barr, Dr. Arthur R. Elliott, Dr. James B. Herick, Dr. Clement R. Jones, Dr. S. Marx White, Dr. Walter L. Bierring, Dr. John H. Musser, Dr. O. H. Perry Pepper, Dr. Francis M. Pottenger, Dr. Luther F. Warren, Dr. William J. Kerr, Dr. Roger I. Lee, Dr. Sydney R. Miller, Dr. George Morris Piersol, Dr. G. Gill Richards, Dr. Ernest B. Bradley and Dr. Maurice C. Pincoffs.

Dr. O. H. Perry Pepper, Chairman of the Committee on Examinations, presented the following report:

"The Committee unanimously is of the opinion that the College should at once take steps toward assuming leadership in the field of the certification of Internists. To this end it recommends to the Board of Regents the following:

"1. The establishment with the Section on the Practice of Medicine of the American Medical Association of an 'American Board for the Certification of Internists' conducted by the American College of Physicians and the Section on the Practice of Medicine of the American Medical Association. This Board to consist of nine members, six to be appointed by the College and three by the Section on the Practice of Medicine of the American Medical Association. Additional members representing other appropriate bodies may be added in the future.

"This Board shall be organized and shall function in accordance with the action of the House of Delegates of the American Medical Association in June, 1934, under the heading 'Essentials for Examining Boards in Specialties.' The rules for qualification of candidates then approved shall be enforced by this Board.

"This Board shall seek the approval of the Council on Medical Education and Hospitals of the American Medical Association according to the resolution of that body on October 27, 1934. In order to obtain such approval the Board must present to that body 'satisfactory evidence of the reliability of their procedure in the examination and certification of candidates' and of the acceptance of the standards adopted by the House of Delegates of the American Medical Association.

"This Board shall be financed from the fees collected, but until such time as this is possible, it shall be financed by loans from the College of Physicians. These loans shall be authorized by the Board of Regents up to a limit of \$10,000 for the first year. Proper expenses for this Board will include traveling and hotel expenses of members, secretarial and office expenses.

"It is assumed that upon approval of the Board by the Section on the Practice of Medicine of the American Medical Association and by the Council on Medical Education the Board will proceed as expeditiously as possible to carry out its function as an examining body for the certification of Internists. Upon its supplying a list of certified Internists to the American Medical Association it is assumed that that body will in the future clearly designate these individuals as Certified Internists in such a manner as to distinguish them from those who merely limit their practice to Internal Medicine.

"It is further assumed that this Board will consider for certification without examination such present Masters and Fellows of the College as the Board of Regents may after careful review recommend. In this respect it is to be pointed out that for some years Fellowship in our College has constituted the only certification of an Internist in this country and that this certification has been based on very excellent criteria.

"2. As a corollary of the establishment of such a Board for the Certification of Internists the Committee recommends to the Board of Regents that every effort be made to raise the standards for Fellowship in every direction and specifically that from the date of the institution of examinations by the Board no Internist shall be eligible for Fellowship unless certified by the examining board as an Internist with the exception of those at present holding Associate membership. With the further exception that the College reserves the right to elect Fellows 'for cause' in exceptional instances. It shall be the aim of the College to raise its standards until it achieves a position analogous to the Royal College of Physicians. Election as a Fellow should indicate distinctly superior qualifications even a further examination than that for certification may some day be instituted for Fellowship.

"Those who at present are Associates shall come up for Fellowship under the custom

existing prior to this meeting, but the hope is expressed that as many as possible will become certified as Internists by examination

"Election to Associateship will continue as at present with, it is hoped, steadily increasing standards and after the Examining Board is functioning efficiently with the inclusion of Certification by that Board as a requirement Associates will still have to qualify for Fellowship within the five year period, and Associates elected after this date will only become eligible to Fellowship after being certified as Internists by the American Board for the Certification of Internists

"The Committee recommends the adoption of this report, the authorization of the Board and its financial support and the appointment by the President of six Fellows of the College to the Board with instructions that they proceed to organize and function as outlined in this report"

Upon motion by Dr Pepper, seconded by Dr G Gill Richards, and regularly carried, it was

RESOLVED, that the above report of the Committee on Examinations be adopted

On motion by Dr James Alex Miller, Chairman of the Committee on Public Relations, seconded by Dr James B Herrick, and regularly carried, it was

RESOLVED, that in view of the fact the Chairman of the Board of Registry of Technicians of the American Society of Clinical Pathologists had requested the endorsement of the American College of Physicians of this Registry and that inasmuch as the Committee on Public Relations of the College had investigated the standing of that Society and found it a splendid, ethical organization and the Board of Registry of Technicians to be serving a very useful purpose of value to physicians generally, a letter to that effect be directed to the Board of Registry offering the cooperation of this College by bringing this service to the attention of its Fellowship when suitable opportunity offers

On motion by Dr James Alex Miller, seconded by Dr Biering, and regularly carried, it was

RESOLVED that a letter be written to the President of the United States urging financial support for the Army Medical Library so that the present retrenchment may be discontinued and the outstanding deficit made up

Reporting for the Committee on Extension of Postgraduate Education, Dr F M Pottenger Chairman said the Committee had met and had approved of the same plan suggested at the last meeting namely, that the matter of sectional meetings for postgraduate training be left with the Board of Governors for each State to decide what particular form of meeting best meets its requirements

By resolution, eight Fellows and eight Associates were dropped for delinquency of two years' standing

By resolution 11 Associates were dropped from the roll because of failure to qualify for Fellowship in the required period of five years

Following the report of the Editor of the ANNALS OF INTERNAL MEDICINE Dr Maurice C Pincoffs a resolution was adopted providing that the office of Associate Editor of the ANNALS OF INTERNAL MEDICINE be established and that a sum not to exceed \$1 200 per year be provided for that purpose the Editor being empowered to nominate to the Committee on the ANNALS the name of an Associate Editor, and the Committee being empowered to accept or reject the nomination

By resolution regularly adopted, it was

RESOLVED that it be the policy of the American College of Physicians not to elect persons to membership who are primarily hospital administrators

May 3, 1935

The third meeting of the Board of Regents was held in the Philadelphia Municipal Auditorium May 3 1935 with Dr James Alex Miller, newly elected President, presiding and with the Executive Secretary acting as Secretary of the meeting The following were present Dr James Alex Miller, Dr Ernest B Bradley, Dr Arthur R Elliott Dr David P Barr Dr Egerton L Crismon Dr William D Stroud Dr Jonathan C Meakins Dr James H Means Dr James B Herrick Dr Charles G Jennings Dr James E Paullin Dr John H Musser Dr Francis M Pottenger Dr Luther F Warren Dr William J Kerr, Dr Roger I Lee Dr George Morris Piersol Dr G Gill Richards Dr Maurice C Pincoffs Dr Charles Hartwell Cocke Dr Charles F Martin, Dr Randolph Lyons, and the Executive Secretary, Mr E R Loveland

A communication from Dr William W Cadbury (Fellow) of Canton China, requesting the College to send a message of greeting and if possible a representative to a conference to be held in Canton, China November 8 1935 commemorating the introduction of scientific medicine in China one hundred years ago by Dr Peter Parker, was referred to the Executive Committee for investigation, with power to act

For the Finance Committee, Dr Charles F Martin, Chairman, reported that the funds of the College were in a gratifying condition, there being a surplus for 1934 of \$16,160 07, as against \$5,801 06 for 1933 and \$10,598 08 for 1932 In accordance with the instructions of the Board of Regents, the funds of the College had been segregated into the Endowment Fund of \$55,720 00 and the balance of \$84,427 10 apportioned to the General Fund The income for 1934 was \$62,000 00 as compared with \$52,000 00 for 1933 The Committee recommended that the Resident Governor for the State of Delaware be constituted the corporate agent for the College in the future, in the place of the Corporation Trust Company The Committee recommended the adoption of the proposed budget of the College for the coming year, adding, however, the additional sum of \$1,200 00 for the expenses of the Editorial Board of the *ANNALS OF INTERNAL MEDICINE*

Upon motions regularly seconded and carried, the following resolutions were adopted

RESOLVED, that the report of the Finance Committee be received

RESOLVED, that the Resident Governor for the State of Delaware, Dr Lewis B Flinn, be constituted the corporate agent of the College, due to the present agent having increased its charges out of proportion to the services rendered

Copies of the financial reports and of the budgets for the coming year were distributed, and the Executive Secretary summarized the salient points With the addition of the item of \$1,200 00 for the Associate Editor, authorized by the Board of Regents at its previous meeting, the total of the 1935 budget was \$52,238 82

Upon motion, seconded and regularly carried, it was

RESOLVED, that the detailed budgets presented be adopted as submitted

In executive session, the Board unanimously voted an honorarium for each of the permanent employees in the College headquarters in consideration of their devoted service and extra labor

Dr William Gerry Morgan, of Washington, was unanimously reelected Secretary-General of the College for 1935-1936

Dr William D Stroud, of Philadelphia, was unanimously reelected Treasurer of the College for 1935-1936

The following Executive Committee was elected for the year 1935-1936

Dr James Alex Miller, *Chairman*

Dr Ernest B Bradley

Dr William Gerry Morgan

Dr William D Stroud

Dr Walter L Bierring

Dr Roger I Lee

Dr James H Means

Dr Maurice C Pincoffs

Dr Francis M Pottenger

In accordance with regulations governing the appointment or election of other Committees, with the exception of the Committee on Examinations and the Committee on Extension of Postgraduate Education, which were discharged with thanks, all other committees were appointed (The personnel of these new committees may be found by consulting page 10 of the June 1935 Issue of the *ANNALS OF INTERNAL MEDICINE*)

The Executive Secretary presented invitations for the 1936 Annual Session from Milwaukee, St Louis and Detroit President Miller reported that in company with the Executive Secretary, Mr Loveland, he had visited St Louis and Detroit to investigate their facilities He and the Executive Secretary both described the comparative advantages of the cities extending invitations After thorough discussion, a vote indicated a preference for Detroit for 1936, and on resolution regularly adopted, the College accepted that City's invitation to hold its Twentieth Annual Session there

Dr David P Barr, Chairman of the Committee on Fellowships and Awards, presented his report, explaining the method of arriving at the Committee's decision on the Fellowship award for the coming year, and announced that after careful consideration, the Committee recommended to the Board of Regents the selection of Dr Michael J Lepore Dr Lepore, now 24 years old, was born in Italy He graduated from the University of Rochester and served his internship at the Duke University Hospital, where he is now working He desires to work with Dr Peters at Yale University Dr Lepore is the author of a number of publications, prepared with and without collaboration, and appears to be a young man of great promise It was the opinion of the Committee that there is an advantage in selecting a man who represents several institutions of learning, rather than one who is in one place and simply requests support for continued work in that same institution

Upon motion by Dr Barr, seconded by Dr Kerr, and regularly carried, it was

RESOLVED, that the Research Fellowship of \$1,800 00 for 1935-1936 be awarded to Dr Michael J Lepore

Upon further motion, seconded and regularly carried, it was

RESOLVED, that this Fellowship should start on July 1, 1935, and that an additional necessary appropriation be made on the budget to take care of the overlapping of two and one-half months with the 1934-1935 Fellowship, which will not expire until September 15, 1935

Dr William D Stroud, Treasurer, submitted the financial reports with the information that the investments of the College have appreciated until they now show a book profit of approximately \$3,000 00 over their purchase price of \$105,828 00, also that the funds of the College had been, for the first time, partially (15 per cent) invested in stocks, with the idea of protecting the investments against inflation

On motion by Dr Barr, seconded by Dr Kerr, and regularly carried, it was

RESOLVED, that a letter of thanks be forwarded to the Orpheus Club of Philadelphia for the excellent concert it had rendered on the occasion of the College Smoker

On motion by Dr William J Kerr, seconded by Dr G Gill Richards, and regularly carried, it was

RESOLVED, that the American College of Physicians make representations to the coming meeting of the Association of American Physicians, acquainting them with the plan of the American College of Physicians for the establishment of a national examining board for the certification of internists, and asking for their comments and cooperation

Adjournment

ANNUAL BUSINESS MEETING

The Annual Business Meeting of the American College of Physicians was held in the Philadelphia Municipal Auditorium, May 2, 1935, with President Jonathan C Meakins presiding, and the Executive Secretary, Mr E R Loveland, acting as Secretary

The Secretary abstracted the Minutes of the previous meeting, which, upon motion, were approved

The Chairman announced that due to illness the Secretary-General, Dr William Gerry Morgan, would be unable to present his report

The Executive Secretary, Mr Loveland, was requested to report on the financial condition of the College, due to the Treasurer, Dr William D Stroud, being delayed The full financial reports, there presented, have been published in the May 1935 Issue of the ANNALS

The Executive Secretary followed this with his own report for the year He announced that the registration at the Philadelphia Session was the largest in the history of the College, being in excess of 2,400 He reported further that 139 Fellows and 244 Associates had been elected since the last Annual Session, also that out of 54 elected to Associateship in 1929, only 10 had failed to qualify for Fellowship, out of 63 elected to Associateship in 1930, 11 had failed to qualify for Fellowship at this meeting In regard to members discontinued from the Roster because of delinquency, there were only 11 Fellows and 15 Associates dropped during 1934, and only 8 Fellows and 8 Associates dropped for delinquency in 1935 This he pointed out was considerably less than 1 per cent of the membership, which is somewhat of an index of the loyalty members feel toward the College, and of the tenacity with which they retain their memberships He reported further that the Executive Offices had handled over 40,000 pieces of mail during the past year, and a total income of about \$62,000 00, that there had been 11 new Life Members, bringing the total up to 47 in all, and that during the coming summer a new and revised Directory of all College members would be published The Executive Secretary thanked the General Chairman, the President of the College and members of the local committees for their help and counsel rendered him in connection with the preparation and conduct of this Annual Session

Dr James Alex Miller was then inducted as President of the College Dr Meakins, in introducing Dr Miller, said, in part,

'It is now my duty, Masters and Fellows, to officially bid you good-bye as your President I expressed my appreciation last evening, and I can only reiterate that again today It has been a great honor and a great pleasure to do anything I could for the College The College has done a great deal for me, and therefore I am not only appreciative but thankful

'I now have a pleasant duty to perform I feel like the high priest and the golden bough I am dead but I hand on the torch to one I know will do the job very much better than I could He is a man beloved by us all respected by us all, and admired for his knowledge his judgment, and what he has done for the medical profession in many of its activities Therefore it gives me great pleasure to hand over the reins of office to my successor, Dr James Alexander Miller, of New York "

In response, Dr Miller said

I think it is useless for anyone to try to express adequately the feeling which must come

on such an occasion as this. Fortunately, the procedure of the College gives one a year to become gradually desensitized from the shock which comes to you when you are first designated as President-Elect. So that I can perhaps, without as much perturbation as would otherwise have been the case, try to express in a very few words what this honor means to me and what I hope I may be able to do for the College.

"It is an extraordinary body of men which we represent, and to be elected to be its presiding officer is an honor second to none, and I appreciate it very much. To follow after those who have gone before is a privilege, but also an overwhelming responsibility. I know that I will not be able to do as well as they, but all that I can say is that my very deepest sympathy is with the interest of the College, and to the utmost of my ability I will do my best to keep on carrying the torch of the College of Physicians in the way that it has been so magnificently carried before.

"I think that we have a great future before us, as well as a magnificent past, and I hope as we go on together that we may, officers and Fellows alike, achieve much that is now in our hearts in the way of hope as well as well earned satisfaction with what has gone before.

"I know that no President of this organization can achieve anything excepting with the support and hearty cooperation of all the Fellowship, all the Governors, and the Regents and particularly, may I say, of the Executive Office, and I think we have an organization in all of these departments of which we are very proud, and upon which I know that I as your presiding officer for the time being will be able to rely with the fullest of confidence. I hope that we will make further progress and I trust that I may during the coming year at least not allow the standards which we have set up to be lowered. I thank you from the bottom of my heart."

President Miller then introduced Dr. George Morris Piersol, who presented a gavel to the retiring President, Dr. Meakins, as a token of the esteem of the College.

Dr. Charles F. Martin, Chairman of the Committee on Nominations, presented the following report:

"The Committee on Nominations, appointed by your President, in accordance with the By-Laws, presents the following nominations:

A For the Elective Officers

<i>President-Elect</i>	Dr. Ernest B. Bradley, Lexington, Ky.
<i>First Vice President</i>	Dr. Arthur R. Elliott, Chicago, Ill.
<i>Second Vice President</i>	Dr. David P. Barr, St. Louis, Mo.
<i>Third Vice President</i>	Dr. Egerton L. Crispin, Los Angeles, Calif.

B For the Board of Regents, term expiring 1938

Dr. Jonathan C. Meakins, Montreal, Que.
Dr. James H. Means, Boston, Mass.
Dr. James B. Herrick, Chicago, Ill.
Dr. Charles G. Jennings, Detroit, Mich.
Dr. James E. Paullin, Atlanta, Ga.

C For the Board of Governors, term expiring 1938

Dr. James F. Churchill	(Southern)	CALIFORNIA, San Diego
Dr. Gerald B. Webb		COLORADO, Colorado Springs
Dr. Henry F. Stoll		CONNECTICUT, Hartford
Dr. Wallace M. Yater		DISTRICT OF COLUMBIA, Washington
Dr. Ernest E. Laubaugh		IDAHO, Boise
Dr. Samuel E. Munson	(Southern)	ILLINOIS, Springfield
Dr. Robert M. Moore		INDIANA, Indianapolis
Dr. Thomas Tallman Holt		KANSAS, Wichita
Dr. William B. Braced		MASSACHUSETTS, Boston
Dr. Adolph Sachs		NEBRASKA, Omaha
Dr. Allen A. Jones	(Western)	NEW YORK, Buffalo
Dr. Leander A. Riely		OKLAHOMA, Oklahoma City
Dr. Edward J. G. Beardsley	(Eastern)	PENNSYLVANIA, Philadelphia
Dr. E. Bosworth McCready	(Western)	PENNSYLVANIA, Pittsburgh
Dr. J. Owsley Mamer		TENNESSEE, Nashville
Dr. Louis E. Viko		UTAH, Salt Lake City
Dr. Jabez H. Elliott		ONTARIO, Toronto, Canada
Dr. William M. James		PANAMA AND THE CANAL ZONE

(Term expiring 1937)

Dr C W Dowden
 Dr Glenville Giddings
 Dr Ramon M Suarez

KENTUCKY, Louisville
 GEORGIA, Atlanta
 PUERTO RICO, San Juan

Respectfully submitted by

Committee on Nominations

DR CHARLES F MARTIN, *Chairman*
 DR ROGER I LEE
 DR WILLIAM J KERR,
 DR CHARLES H COCKE,
 DR GERALD B WEBB "

Upon motion duly seconded, the report of the Nomination Committee was adopted unanimously, and the persons named declared duly and unanimously elected

Dr S Marx White presented the following report for the Committee on Resolutions

"I move that an expression of appreciation be spread on the Minutes to recognize the extraordinary character of the Session provided in this cradle of medical education in America and that special mention be made of the service of Dr Alfred Stengel, Chairman, and his Committee on Arrangements, Dr O H Perry Pepper, Chairman, and his Committee on Clinics, Dr Thomas Fitz-Hugh, Jr, and the Committee on Morning Lectures, Dr Robert G Torrey and the Committee on Auditorium, Dr Richard A Kern and the Committee on Publicity, Dr Harry B Wilmer, the Orpheus Club, and the Entertainment Committee, Mrs George Morris Piersol, Chairman of the Committee on Entertainment of Visiting Women, as well as the medical profession of Philadelphia represented by the Philadelphia College of Physicians and the Philadelphia County Medical Society, also, the Convention Bureau of the Chamber of Commerce"

The motion was seconded and carried unanimously

There being no further business, the meeting adjourned at 5 10 p m

ANNALS OF INTERNAL MEDICINE

VOLUME 9

AUGUST, 1935

NUMBER 2

THE ACUTE COR PULMONALE *

By PAUL D WHITE, M D , F A C P , *Boston, Massachusetts*

THE limits of the field of simple clinical observation have not yet been reached. There are still puzzles to solve and new observations to make at the bedside itself or in the office and without the need of elaborate apparatus or extensive knowledge of chemistry or physics. I shall relate to you today an interesting experience of my own and its development by Dr. Sylvester McGinn and myself, in the field of clinical observation, which has resulted in an advance of our knowledge in internal medicine. The new ground which we have occupied is still in a rough condition and needs to be further explored and consolidated. We have searched the literature but have found only statements indicating that this is a direction in which an advance is needed and the mention of some of the signs that we have grouped together. I shall come back to these statements later on.

Case 1 On October 20, 1932, two and one-half years ago, I was asked to see a professor, 42 years old, who was suffering from an acute complication during his convalescence from a surgical operation, which had consisted of the removal of a gangrenous appendix with the establishment of drainage. The day before my examination, which was 30 days after the operation, he was suddenly seized with substernal distress and dyspnea, his pulse rate rose to 130, and his blood pressure fell to 90 millimeters systolic and 70 diastolic. When I examined him I found his skin slightly pale and cyanotic, his heart apparently normal in size but with poor sounds at the apex, marked accentuation of the pulmonary second sound, visible and palpable systolic pulsation in the second left intercostal space near the sternum over the pulmonary artery, and a slight to and fro friction rub just at the left of the sternum in the third and second intercostal spaces. The pulse rate was 100, the blood pressure 120 systolic and 90 diastolic, and the temperature was 100.8°, the respiratory rate was 35 to 40, and the leukocyte count had risen from 12,800 of the day before to 28,000. His electrocardiogram taken two hours after the attack of October 19 showed sinoauricular tachycardia with prominent S-waves and slightly low origin of the T-waves in Lead I, low T-waves with gradual ascent in Lead II, and deep Q-waves and late inversion of the T-waves in Lead III. A tentative diagnosis of acute coronary thrombosis was made. The next day he was still very ill, there was now an increased venous pulse in the neck, the friction rub was diminished, and signs of pulmonary infarction on physical examination (dullness and bronchial breathing) and by roentgen-ray had developed at the angle of the right scapula. The diagnosis was

* Read at the Philadelphia meeting of the American College of Physicians, May 2, 1935

changed to extensive pulmonary embolism with acute dilatation of the right heart (the acute cor pulmonale) Helpful in establishing this diagnosis were two other episodes during convalescence from the operation, both of which were obviously pulmonary infarcts of moderate but not high degree, one on the ninth and the other on the forty-ninth postoperative day, four days after the first pulmonary infarct a phlebitis of the right lower leg became evident There was no further trouble and the patient was discharged to his home 94 days after the operation in good health and with a normal electrocardiogram He has remained well since

Three other cases illustrating various features of this subject are worthy of brief note before we consider in detail the signs of the acute cor pulmonale

Case 2 A merchant, 48 years old, consulted me on August 29, 1933, because of two attacks which had suggested to his family doctor some trouble with his heart Four weeks before, he had been seized by epigastric pain extending up into the left chest but not preventing him from driving his car 200 miles He spent one day in bed and then resumed work although the left chest pain persisted in decreasing degree for a week, aggravated by deep breathing Twelve days after the first attack and while preparing breakfast he was seized by a clutching sensation or catch in the throat with difficulty in breathing His doctor gave him morphine and put him to bed for five days Ten days after getting up and about he came to see me, feeling very well Examination showed nothing amiss, except that his tongue was slightly coated, his pulse rate was 96, fluoroscopy showed the heart slightly enlarged transversely with undue prominence of the pulmonary artery, and somewhat cloudy lung fields, and the electrocardiogram showed low T-waves in all leads Recent past history revealed one very significant fact—a severe sprain of his leg on playing tennis four weeks before his first attack of chest pain, he had been laid up with swelling of the leg for about a week Eight days after my examination the patient had a sudden collapse with dyspnea of unknown nature and died in the course of a few hours Postmortem examination showed moderate dilatation and hypertrophy of the right ventricle with heart weight of 400 grams with no evidence of valvular, coronary, or pericardial disease but with multiple infarcts, in the lungs, a small one in the right upper lobe, another small one in the left upper lobe, a large one in the left lower lobe with laminated clot partly occluding the main left pulmonary artery and with a fresh clot superimposed upon it

Case 3 On June 4 of last year, 1934, I was asked to see a lawyer who had been taken seriously ill the night before with an attack of substernal oppression radiating partway out to the right axilla, lasting for hours, attended by exhaustion, dyspnea, and sweating and only partly relieved through the night by repeated doses of morphine At 4 a m he grew desperately ill with marked cyanosis and dyspnea The doctor in attendance found then a to and fro friction rub at the left of the upper sternum and a diastolic gallop rhythm in the midprecordial region He administered oxygen and carbon dioxide with great benefit When I examined the patient at 11 a m he was already much improved but he showed still some dyspnea and cyanosis and his jugular veins were moderately distended and pulsating The pulmonary second sound was accentuated and doubled but the gallop rhythm and precordial friction rub had gone Dullness and pleural friction rub were present in the right axilla The patient rapidly recovered and in a few weeks was in good health and back at work Recent past history revealed a milder but otherwise similar episode with chest pain on the left one week before his severe attack and a phlebitis of his right calf after a strain while working in his garden a week before that

Case 4 Early in January of this year a man, 41 years old, entered the surgical service at the Massachusetts General Hospital because of upper abdominal pain

Examination showed normal heart and blood pressure. A diagnosis of gall stones was made and the gall-bladder containing several small stones was removed. On the twenty-fifth postoperative day there was sudden epigastric and lower substernal distress with great dyspnea. A state of shock followed, with ashy cyanosis, cold sweat, rapid, thready pulse and a drop in blood pressure to 75 mm systolic and 60 diastolic. After a few hours the shock lessened and examination showed a to and fro friction rub at the left of the upper sternum and a loud diastolic gallop rhythm at the lower end of the sternum. The diagnosis rested between acute coronary occlusion and the acute cor pulmonale due to extensive pulmonary embolism. The next day both friction rub and gallop rhythm had disappeared and the patient complained of pain in the right chest and coughed up blood-tinged sputum. Roentgen-ray showed a triangular area of dullness in the right lung that was evidently a pulmonary infarct. An electrocardiogram taken 10 hours after the attack showed prominent S-waves in Lead I, low T-waves in Lead II, prominent Q-waves and inverted T-waves in Lead III, and upright T-waves in Lead IV (the precordial lead). Twenty-five days after the attack and four days before discharge from the hospital in good condition the electrocardiogram showed a considerable change with no S-waves in Lead I, normal T-waves in Lead II, no Q-waves and flat T-waves in Lead III, and flat T-waves with deeper Q-waves in Lead IV.

These four cases illustrate well the various features of what I would call the *acute cor pulmonale*, that is, dilatation of the pulmonary artery and right heart chambers with or without failure, which results from a sudden great obstruction to the pulmonary circulation, best exemplified by massive pulmonary embolism. There have been 10 other cases which have come to our observation in the past two years which have shown some of the features noted in the four cases I have cited above. In all of these 14 cases the diagnosis of pulmonary embolism was confirmed either by autopsy, in five of the six fatal cases, or by adequate clinical evidence, including roentgen-ray examination. Only rarely, however, are all the signs and symptoms that may be said to mark the acute cor pulmonale present in the same case at the time of observation. To encounter a case with just the right amount of pulmonary arterial obstruction at just the right time is rather a fortuitous occasion and yet doubtless not very rare in the work of any physician in active medical or surgical practice. It has not been difficult for us to come across these 14 cases of ours in the short period of two and one-half years.

If the pulmonary arterial obstruction is too overwhelming and complete, either death may ensue quickly or a serious state of shock which depletes the circulation and prevents the overburdening of the right heart. In such cases the signs of the acute cor pulmonale are missing until after the state of shock has subsided. If, on the other hand, the embolus is small or of only moderate size, blocking only one large or small pulmonary arterial branch or several small branches, the obstruction may be too slight to dilate the right ventricle. Experiments on animals have shown that the right heart can stand the strain of the blocking of either one of the two pulmonary arteries without dilating, that is, without the occurrence of the acute cor pulmonale. Finally, the existence of the maximum stage of the acute strain on the right heart may be brief, a matter of hours sometimes, rather than

days, and then the physician may make his examination only after the acute cor pulmonale has in large part or wholly subsided. With these points in mind let us now turn to the diagnosis of this condition.

DIAGNOSIS OF THE ACUTE COR PULMONALE

1 *The Recent Circumstances* Of great help in the diagnosis of pulmonary embolism, which is the cause of the acute cor pulmonale, is the knowledge of the recent history of the patient. A surgical operation, especially one involving abdomen or pelvis, an accident causing fracture or strain, especially of the legs, and a past or recent phlebitis even in the absence of operation or accident are very significant in differential diagnosis. Infrequently, if the patient has heart disease the source of the embolus may be the right auricle itself. The acute cor pulmonale is more commonly found in middle aged and old persons than in youth.

2 *Onset* The onset is abrupt and in that respect resembles acute coronary occlusion and dissecting aortic aneurysm from which it must be differentiated. Dyspnea is more common as the first symptom than is thoracic oppression but substernal oppression alone or accompanying dyspnea is not a rare complaint and may be misleading. Vasomotor shock with ashy pallor, thready pulse, low blood pressure, and cold sweat, is common at the onset, as it is in numerous other serious conditions. Pain in the side of the chest from pleurisy is not the earliest symptom and sometimes is delayed for many hours.

3 *Early Signs* Frequently examination of the lungs shows no definite abnormalities in the first 12 to 24 hours or even longer after pulmonary embolism, and the roentgen-ray too may help but little at first although a high position of the diaphragm is suggestive.

When, however, the embolism is massive enough to cause a dilatation of the right heart—the acute cor pulmonale—certain early signs of such a phenomenon may appear. These are as follows:

(a) *Increased prominence and pulsation, noted by inspection and palpation, in the region of the second and third intercostal spaces just to the left of the sternum* and overlying the dilated and sometimes overactive pulmonary artery and conus (infundibulum) of the right ventricle. There may be also a loud systolic murmur and a much accentuated pulmonary second sound if the circulation is not too much obstructed. We have not heard a diastolic murmur.

(b) *Friction rub* in this same region, that is, in the second and third intercostal spaces just to the left of the sternum, to and fro in time in some cases, in others apparently with systole alone. It is this sign which has most often caused an erroneous diagnosis of coronary thrombosis. The explanation of this friction rub is not certain, but is doubtless to be sought in marked engorgement of the pulmonary artery and right ventricular infundibulum strongly impinging on the anterior thoracic wall. A somewhat

similar friction rub has been noted in a few cases of thyrotoxicosis with marked increase in the pulmonary circulation and dilated pulmonary arteries

(c) *Gallop rhythm*, diastolic in time, heard along the left sternal border, and presumably due to dilatation of the right ventricle, much as the common protodiastolic gallop rhythm at the apex attends left ventricular dilatation and failure

(d) *Dilatation and increased pulsation of the jugular veins* If the pulmonary obstruction and strain on the right ventricle are of sufficient degree to cause a damming back of blood behind the right auricle the jugular veins become engorged, and pulsation may be evident in them even with the head and neck elevated at a high angle. Such a sign should not be confused with heart failure following coronary thrombosis, which incidentally is first manifested by pulmonary congestion and edema and rarely results in failure of the whole heart sufficiently early to give rise to engorgement of the jugular veins such as can easily take place from pulmonary embolism in the first few hours after the onset of trouble. We have rarely encountered enlargement of the liver in the cases of the acute cor pulmonale, perhaps because there is hardly enough time—a matter of hours—for its development

(e) *Cyanosis* The cyanosis which is commonly seen in cases of pulmonary embolism in contrast to cases of coronary thrombosis, is doubtless accentuated when the right heart fails and obstruction to blood flow involves the great veins

4 *Course* The cardiovascular signs of the acute cor pulmonale may subside quickly, in the course of hours, or last for days until death or recovery takes place. Eight of the 14 patients that we have observed have recovered

Twelve hours or more after the onset of the pulmonary embolism fever and leukocytosis are found and their presence may further confuse the picture with that of coronary thrombosis. But usually by the time these developments have taken place lung symptoms and signs begin to appear—cough with bloody sputum or pleural pain with friction rub or signs of localized consolidation (infarction) by physical examination or roentgen-ray. There may also be a delayed appearance of a phlebitis in the leg responsible for the pulmonary embolism, or such a lesion may be found before the accident or at the time

One of the peculiarities of pulmonary embolism, postoperative or otherwise, is that it is very likely to recur, sometimes frequently over a period of weeks. Such recurrence at frequent or short intervals is rare in the case of coronary thrombosis, and should at once put us on our guard about the diagnosis

5 *Roentgen-Ray Evidence* There exists as yet no roentgen-ray evidence of the acute cor pulmonale. It is difficult to obtain such evidence and we have yet to try to get it. We expect that when films are secured at the height of the trouble they will probably show in oblique or lateral views bulg-

ing anteriorly of the engorged right ventricle, and in anteroposterior views prominence of the pulmonary artery and of the right ventricular infundibulum, just below it and in some cases an increased transverse cardiac diameter mainly the result of dilatation of the right auricle

So far as the pulmonary infarction is concerned roentgen-ray evidence as already noted above is often lacking at the first during the acute stage, but when it does develop it is naturally of fundamental diagnostic importance

6 *Electrocardiographic Evidence* Finally, to prove perhaps most important of all, is the electrocardiogram of the acute cor pulmonale. At the beginning of our study this was a source of confusion. The changes were slight but misleading, consisting of lowering, flattening, or even slight inversion of the T-waves in Lead II, inversion of the T-waves in Lead III, wide or deep S-waves in Lead I and inversion of QRS waves in Lead III. The records suggested those found with small areas of infarction at the base of the left ventricle behind due to occlusion of the right coronary artery—the so-called coronary T_3 type. With the subsidence of the condition, however, the electrocardiograms quickly became normal. As time went on we began to take Lead IV, the chest lead, with right hand electrode applied to the precordium midway between sternum and nipple line. To our surprise we found in this record an upright T-wave with relatively normal P and QRS waves, with return to normally inverted T-waves when the acute cor pulmonale subsided. The points of particular interest about this record are that it differs from the Lead IV of coronary thrombosis of either of the common (that is, T_1 or T_2) types, and that it is in agreement, so far as the T-wave is concerned at least, with Lead IV in mitral stenosis or the tetralogy of Fallot where the right ventricle is known to be enlarged. It is too soon as yet to state whether or not Lead IV of the electrocardiogram will prove to be the pathognomonic sign of the acute cor pulmonale. Many more records are needed.

In the *differential diagnosis* of the acute cor pulmonale the four conditions that are to be particularly considered are coronary thrombosis, dissecting aortic aneurysm, pulmonary collapse, or spontaneous pneumothorax, and pulmonary edema from heart disease with or without cardiac asthma. Only the first and last are both common enough and difficult enough to require special consideration, and such consideration of coronary thrombosis I have given in my discussion above on diagnosis. An additional point of importance favoring the diagnosis of coronary thrombosis is a past history of angina pectoris present in about half the cases. Finally, as an acute emergency pulmonary edema with or without cardiac asthma may simulate severe pulmonary embolism. The absence of any evidence of important heart disease before the attack, in the form of aortic valve disease, hypertensive heart disease, recent coronary thrombosis, or marked mitral stenosis helps to rule out pulmonary edema of cardiac origin and cardiac asthma.

Treatment The treatment of the acute cor pulmonale is, in part, that

of the underlying disease, namely pulmonary embolism, which in very severe cases may necessitate the attempt at pulmonary embolectomy. In somewhat doubtful cases, before proceeding with this serious operation, it should prove very helpful to obtain further confirmation of the diagnosis by the finding of various signs of the acute cor pulmonale that I have presented above. Whether or not digitalis may be helpful in supporting the right ventricle in its strenuous work in these cases I do not know, I see no reason why it should not be given in fairly full but not toxic doses. Much time may elapse before we can obtain accurate information on this point. Venesection, when there is not a state of shock, may also be worth consideration in selected cases.

Literature Only a few words need be said about the literature on this subject. So far as I know the first mention of the clinical recognition of the acute cor pulmonale, though not called by that name, was in a paper published by Oscar Brenner and myself¹ in the *New England Journal of Medicine* on December 21, 1933. A fairly full discussion of the subject, under the title of "The Acute Cor Pulmonale," by Sylvester McGinn and myself² has just appeared in the *Journal of the American Medical Association*. Otherwise one finds in the literature accounts of animal experimental work on occlusion of the pulmonary circulation and its effects, as by Cohnheim,³ Mann,⁴ Haggart,⁵ Moore and Binger,⁶ Churchill,⁷ and their associates, brief references, at increasingly shorter intervals now, concerning the difficulties of differential diagnosis clinically between coronary thrombosis and pulmonary embolism, best exemplified by recent papers of Hamburger,⁸ of Averbuck,⁹ and of Hamman,¹⁰ without especial reference, however, to the acute cor pulmonale, and finally a mention of some of the individual signs as by Litten¹¹ and Lord.¹² I hope that we have now somewhat clarified this difficult question.

CONCLUSION

The clinical recognition of the acute cor pulmonale—dilatation of the pulmonary artery and right heart chambers with or without failure—is an important step in the early differentiation between massive pulmonary embolism and coronary thrombosis or other conditions. Such recognition is of great importance in ultimate prognosis and may have significant bearing on emergency treatment. Evidence of the acute cor pulmonale has been presented above from the analysis of 14 cases.

REFERENCES

- 1 WHITE, P. D., and BRENNER, O. Pathological and clinical aspects of the pulmonary circulation, *New Eng Jr Med*, 1933, ccix, 1261-1265.
- 2 MCGINN, S., and WHITE, P. D. Acute cor pulmonale resulting from pulmonary embolism, its clinical recognition, *Jr Am Med Assoc*, 1935, civ, 1473.
- 3 COHNHEIM, J. F. Lectures on general pathology, 1889-1890, i, 54, New Sydenham Society, London.

- 4 MANN, F C An experimental study of pulmonary embolism, Jr Exper Med, 1917, xvi, 387
- 5 HAGGART, G E, and WALKER, A M Physiology of pulmonary embolism as disclosed by quantitative occlusion of the pulmonary artery, Arch Surg, 1923, vi, 764-783
- 6 MOORE, R L, and BINGER, C A L Observations on resistance to the flow of blood to and from the lungs, Jr Exper Med, 1927, xlv, 655-671
- 7 CHURCHILL, E D The mechanism of death in massive pulmonary embolism, Surg, Gynec and Obst, 1934, lx, 513-517
- 8 HAMBURGER, W W, and SAPHIR, O Pulmonary embolism complicating and simulating coronary thrombosis, Med Clin N Am, 1932, xvi, 383-403
- 9 AVERBUCK, S H The differentiation of acute coronary artery thrombosis from pulmonary embolization, Am Jr Med Sci, 1934, clxxvii, 391-401
- 10 HAMMAN, L Remarks on the diagnosis of coronary occlusion, ANN INT MED, 1934, viii, 417-431
- 11 LITTEN, M Über Verengerungen im Stromgebiet der Lungenarterie, über deren Folgen und die Möglichkeit, dieselben während des Lebens zu diagnosticiren, zugleich ein Beitrag zur Lehre von der ungleichzeitigen Contraction bei der Herzkammern, Berl klin Wchnschr, 1882, xix, 425, 443
- 12 LORD, F T Diseases of the bronchi, lungs, and pleura, 1925, Lea and Febiger, Philadelphia, p 483-484

EFFECT OF VIBRATORY STIMULATION ON THE NEUTROPHILIC INDEX ¹

By JAMES C HEALY, MARION H SWEET and FELIX P
CHILLINGWORTH, F A C P, *Boston, Massachusetts*

WHILE studying blood smears during the experimental production of eosinophilia,¹ the authors observed that electrical stimulation caused marked alteration in the character of neutrophils in the circulating capillary blood. This stimulation produced an increase in the percentage of young neutrophils which was relative and absolute.

According to Arneth,² the neutrophils in the peripheral blood can be differentiated. He described several classes which are based on the theory of the successive development of a greater segmentation of the nucleus with age. Cooke and Ponder³ have simplified this classification by establishing five major groups or types, the first being the youngest, and the fifth, the oldest circulating neutrophile. In their Type I neutrophile, the several parts of the nucleus are connected by a band of chromatin wider than a filament. The Type II neutrophile has a filament connecting two nuclear lobes. Type III is characterized by three lobes with connecting filaments. Type IV has four lobes with connecting filaments, and Type V has five or more lobes and uniting filaments. Their normal 'neutrophile formula' is as follows:

Type I	II	III	IV	V
10	25	47	16	2

The figures represent the numbers of each form in 100 circulating neutrophils.

Emphasis has been placed by Schilling⁴ on the clinical interpretation of this 'neutrophile formula'. An increase of the first two types, particularly the first, and a decrease of the others constitute the "shift to the left" which is peculiar to certain infections. Depending upon the extent of the "shift to the left," the severity of some infectious diseases and their prognoses can be estimated.

For electrical stimulation, we used induced current having a rate of 3600 vibrations per minute. The electrodes were firmly held in the hands and the intensity of the shocks was felt in the entire forearm. The period of stimulation was four minutes.

In each experiment, blood smears were taken immediately before, at the end of the stimulation period, 15 minutes later and lastly 30 minutes after stimulation.

Table 1 presents the total leukocyte counts, differential counts, and the Cooke and Ponder formulae of nine normal and of one abnormal young male.

* Received for publication April 26, 1935.

From the Department of Pharmacology, Tufts Medical School.

adult All these determinations were made between two and three o'clock in the afternoon The leukocyte and differential counts were ascertained in the usual ways The classification of the several neutrophils was obtained by examination of especially stained specimens

TABLE I

	Total WBC	% Pol. nuclears	% Type I (Arneht)	% Type II (Arneht)	% Type III (Arneht)	% Type IV (Arneht)	% Type V (Arneht)	% Large Lymph	% Small Lymph	% Mono-cytes	% Transi-tionals	% Baso-philes	% Doso-philes	Absolute No. Type I per cu mm
Pt 1 Normal	8350	83	8.3	17.7	36.0	18.0	4.0	4.0	14.6	4.3	0.0	0.0	0.0	69
4' Stimulation	9350	66.3	26.7	16.6	12.6	7.7	2.7	10.6	12.6	7.7	1.3	2.0	4.0	2506
15' Later	9000	71.0	19.7	26.0	16.7	7.3	1.3	8.0	14.6	6.0	0.0	0.0	0.6	1773
30' Later	8600	74.0	18.0	26.0	20.0	8.0	2.0	6.0	10.6	3.3	0.0	0.0	2.0	1548
Pt 2 Normal	9000	60	4.0	10.0	20.0	22.0	4.0	14.0	16.7	4.3	5.7	0.6	2.0	360
4' Stimulation	11450	63	16.0	20.0	15.0	10.0	2.0	12.0	19.0	7.0	4.0	0.0	1.0	1832
15' Later	10200	68	6.0	16.0	24.0	16.0	6.0	13.0	12.0	1.0	4.0	0.0	1.0	612
30' Later	9800	70	4.0											392
Pt 3 Normal	5650	70	2.0	10.0	24.0	23.8	10.2	6.7	13.3	4.6	4.6	0.0	1.7	113
4' Stimulation	7150	65.5	12.5	18.0	20.0	13.0	2.0	10.5	15.0	5.5	2.0	0.0	0.0	894
15' Later	6800	70	10.0	14.0	22.0	20.0	4.0	6.7	13.3	4.3	0.7	0.0	1.7	680
30' Later	6400	73	7.0											448
Pt 4 Normal	8200	54.14	0.68	7.16	31.4	13.6	1.3	6.12	27.9	3.7	0.34	0.0	1.02	56
4' Stimulation	10800	66.5	19.0	22.5	23.5	3.5	0.0	7.0	19.0	3.5	0.0	0.0	2.5	2052
15' Later	9600	54.2	8.4	20.1	29.2	6.5	0.0	9.1	18.2	3.9	1.3	0.0	2.5	806
30' Later	9200	64.7	6.68	18.42	28.6	8.4	2.1	6.8	20.4	3.8	1.0	0.0	4.1	614
Pt 5 Normal	6600	74.6	1.53	12.2	41.3	18.3	1.5	3.1	12.2	6.1	1.5	0.0	1.5	101
4' Stimulation	8400	75.35	19.90	20.0	24.8	9.85	0.8	1.65	11.4	8.6	2.8	0.0	0.0	1670
15' Later	8000	76.54	10.34	14.84	34.78	16.58	0.0	2.7	12.56	4.8	2.1	0.0	1.0	827
30' Later	7400	77.77	8.60	13.42	34.8	18.52	2.4	3.0	10.8	4.0	2.0	0.0	1.0	636
Pt 6 Normal	5000	43.8	0.6	6.6	20.0	10.0	6.6	13.3	33.0	10.6	10.0	0.6	1.3	30
4' Stimulation	5750	60.2	10.0	19.6	16.0	10.6	4.0	10.6	10.6	8.0	10.0	0.0	1.3	575
15' Later	5600	50.3	5.0	9.6	23.8	14.7	7.2	11.0	7.8	6.8	11.0	0.0	1.8	280
30' Later	5200	61.0	4.0	8.0	30.0	12.0	7.0	8.0						208
Pt 7 Abnormal	14200	7.4	0.0	2.8	3.7	0.9	0.0	6.5	15.3	0.9	0.9	0.0	69.0	0
4' Stimulation	15000	6.5	2.8	2.8	0.9	0.0	0.0	2.7	6.3	2.8	2.8	0.9	77.0	420
Pt 8 Normal	7600	68.4	1.6	17.1	35.7	10.5	3.5	7.2	18.7	1.7	1.5	1.0	1.5	122
4' Stimulation	9100	61.8	9.53	17.65	25.72	8.9	0.0	5.15	22.8	8.82	1.54	0.0	0.0	870
15' Later	8800	62.75	7.8	19.65	24.8	9.0	1.5	6.0	24.0	6.4	1.5	0.0	0.0	686
Pt 9 Normal	8600	72.2	6.2	16.4	32.6	14.2	2.8	2.2	15.8	1.0	1.2	0.0	0.0	533
4' Stimulation	10400	63.0	16.4	18.2	22.3	4.5	1.6	7.3	11.4	8.2	6.4	1.5	0.0	1712
15' Later	9800	70.3	12.1	22.0	27.2	7.0	2.0	7.2	14.4	4.6	2.0	1.0	0.0	1186
30' Later	9200	71.8	9.2	21.6	30.4	8.2	2.4	7.0	15.4	3.2	1.5	1.1	0.0	846
Pt 10 Normal	8400	75.4	0.8	10.0	41.0	12.6	1.0	3.0	26.0	3.0	3.0	0.0	0.0	7
4' Stimulation	10800	75.6	20.6	18.0	29.0	7.0	1.0	9.0	11.0	3.5	3.0	0.0	0.0	2225
15' Later	9600	81.3	14.2	20.6	30.0	14.0	2.5	4.0	13.0	2.0	1.0	0.0	0.0	1363
30' Later	8800	79.6	9.4	24.2	28.0	12.0	6.0	3.0	16.0	1.5	0.5	0.0	0.0	827
Average (Normal)	7710	67.17	2.88	10.99	28.57	14.39	3.49							132
4' Stimulation	9240	66.47	16.74	17.33	18.98	7.51	1.41							1593
15' Later	8600	67.15	10.38	18.08	25.73	12.42	2.45							912
30' Later	8075	71.48	7.86	18.60	28.63	11.20	2.34							689

Study of the averages in table 1 reveals that before stimulation only 132 of the 5179 neutrophils are of the first or youngest type. Immediately after stimulation there is only an increase of 1500 neutrophils of all types, whereas there is an absolute increase of 1461 Type I neutrophils. The difference must represent older leukocytes which have been either removed from the circulating blood or greatly dispersed by the influx of the younger forms.

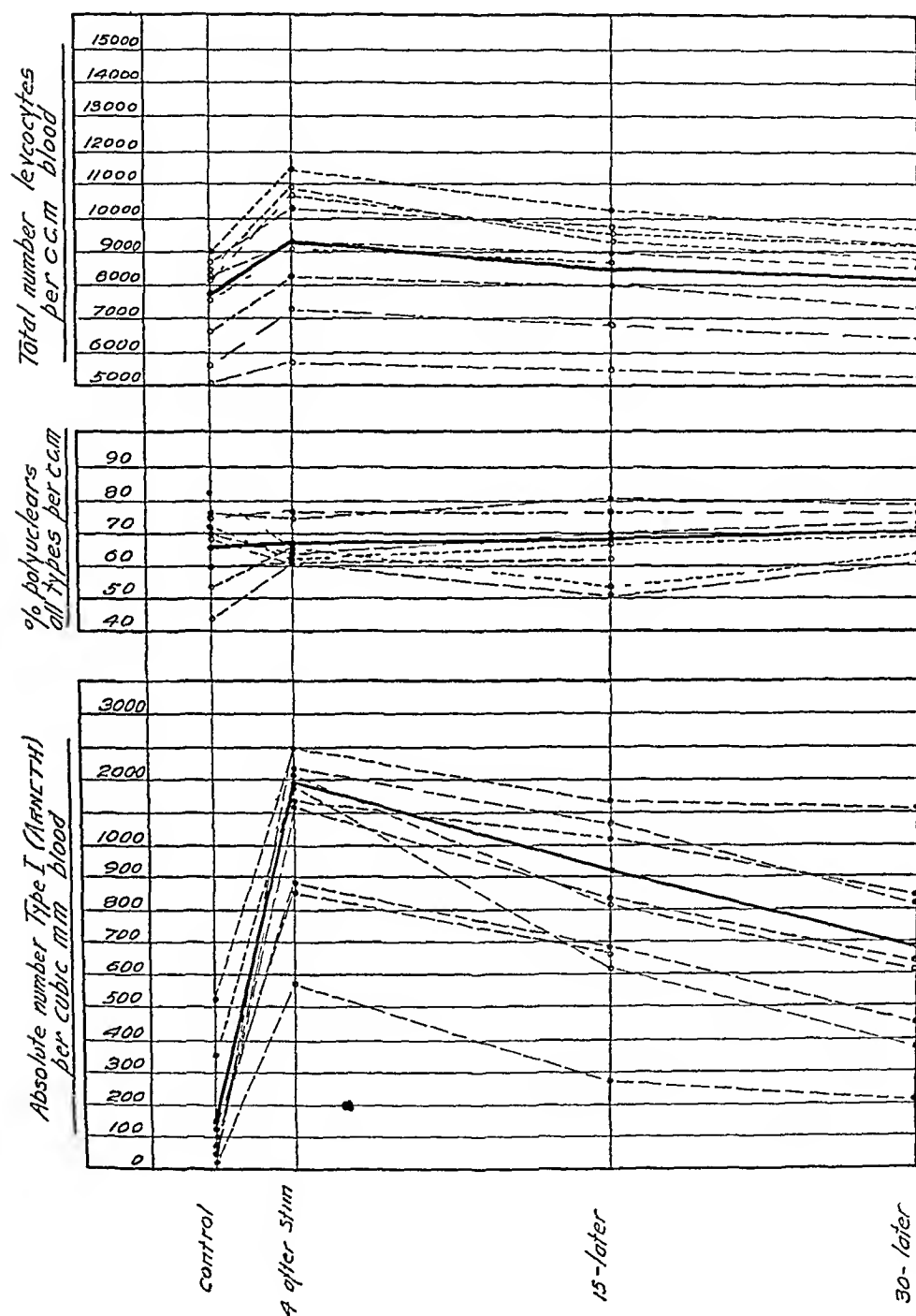


FIG 1

That is, at least 1461 young neutrophils have appeared suddenly in each cubic millimeter of peripheral blood and displaced the older forms. Table I also demonstrates a similar absolute and relative increase of Type II neutrophils, but the change is not so striking.

Blood analyses of several subjects showed that the Type I neutrophilia persisted for several days. Three had a Type I neutrophile increase of 3 to 5 per cent above the original count for 4 days. Furthermore, it was found that when these individuals were re-stimulated, the Type I neutrophilia at the end of four minute stimulation exceeded that of the first day by 10 to 12 per cent.

Figure 1 demonstrates graphically the type of curve following stimulation with induced current. Even though the total leukocyte count and the absolute number of Type I neutrophils rise and fall sharply, the differential count line remains practically flat.

Comparison of the results obtained by electrical stimulation with the effects of mechanical vibration was next investigated. For this purpose, two commercial massage vibrators were utilized—one with a rate of 4200 vibrations per minute, and the second with a rate of 7200 per minute. The subjects, by tightly grasping the vibrating instrument, were stimulated four minutes.

In table 2 are tabulated the blood changes resulting from mechanical stimulation with a rate of 4200 vibrations per minute. The same technic was followed as outlined in table 1. With this vibrator the average increase of total leukocytes was 38.8 per cent and the increase of neutrophils of all types was 3.17 per cent. There was an absolute increase of 11.44 per cent Type I neutrophils. Figure 2 graphically shows these changes.

TABLE II

[illegible]

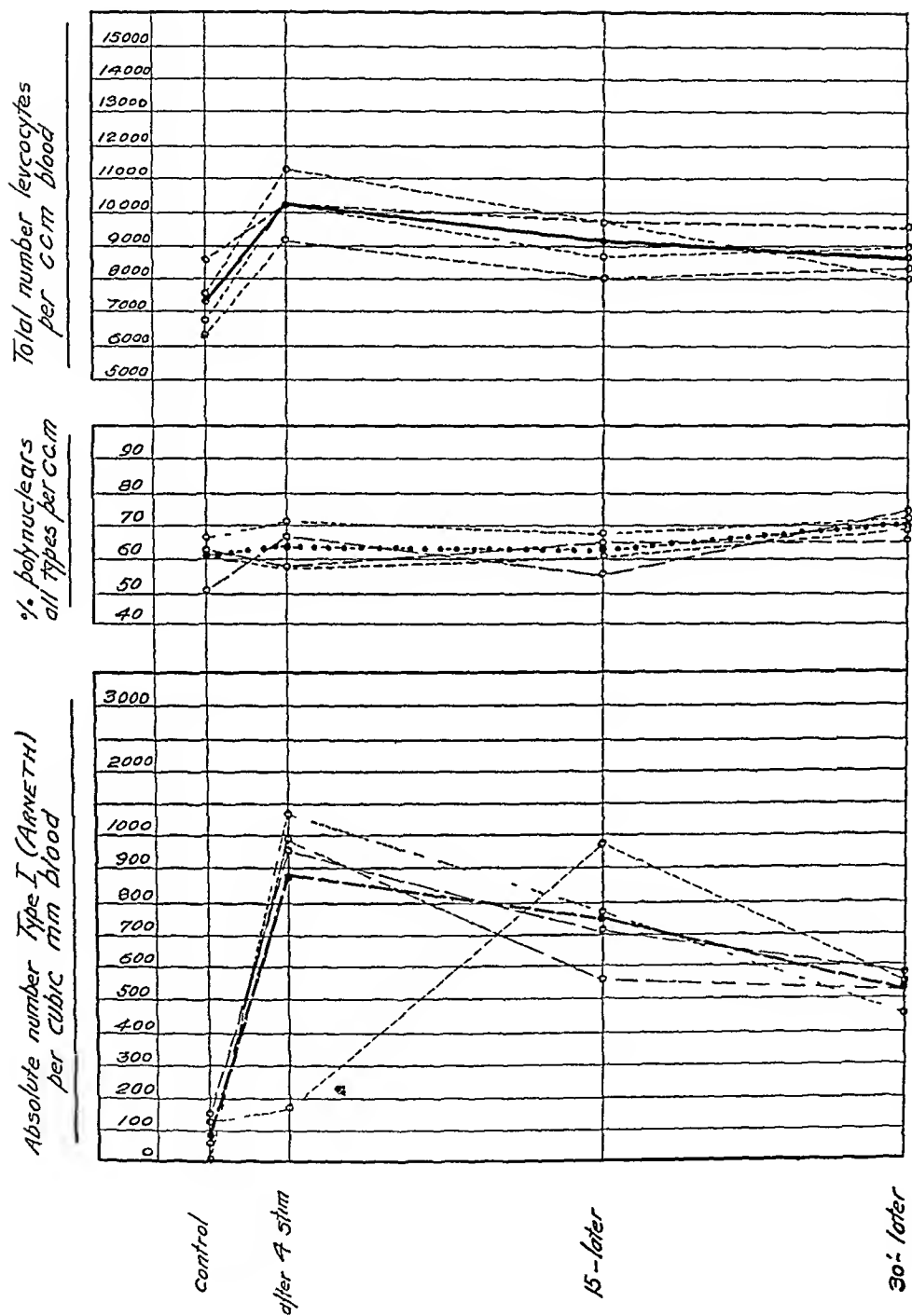


FIG 2

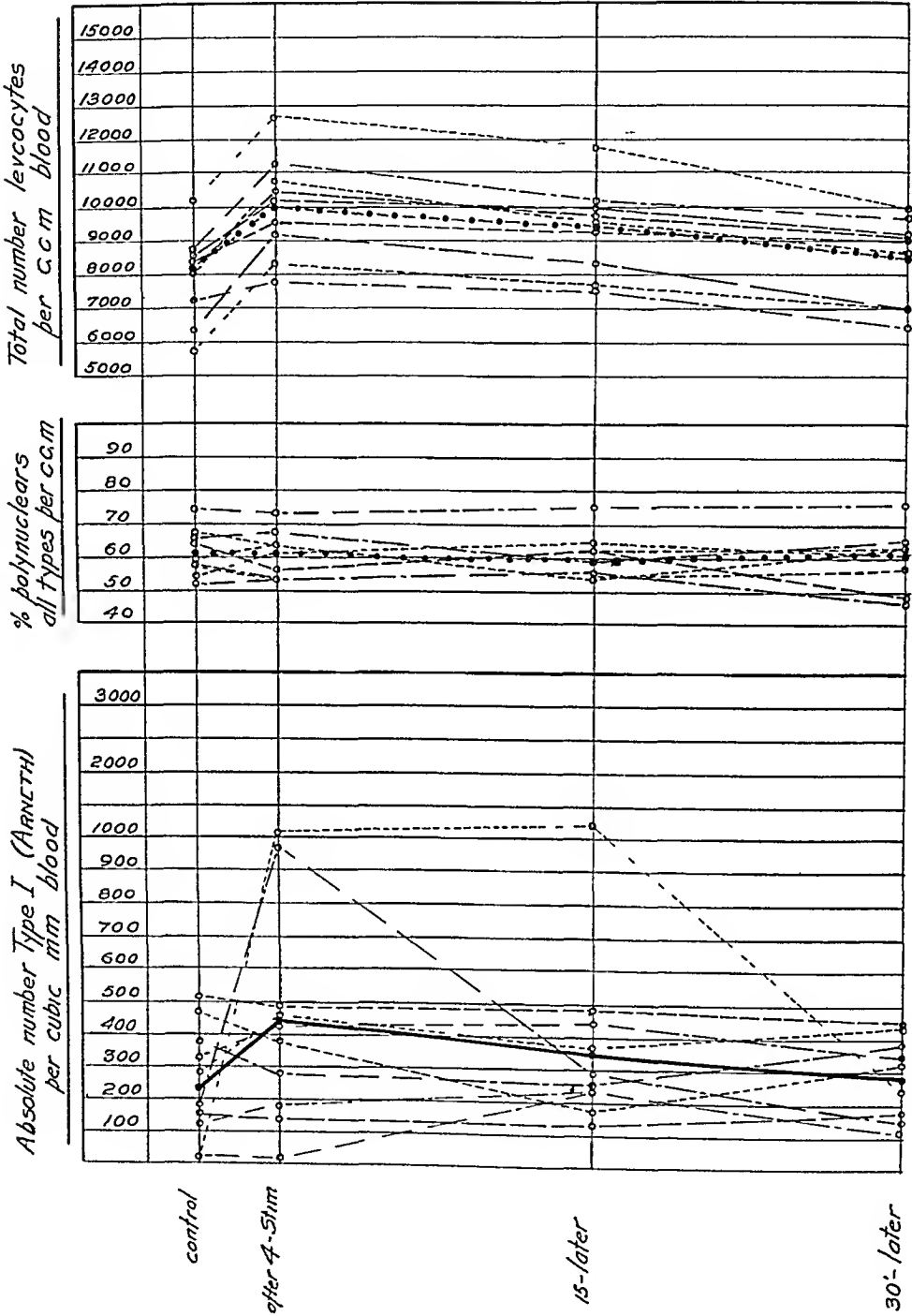


FIG 3

The results of stimulating the hands and forearms of five elderly people (over 70 years of age) are recorded in table 4. Figure 4 represents graphically the alteration of total white counts, polynuclear percentages, and

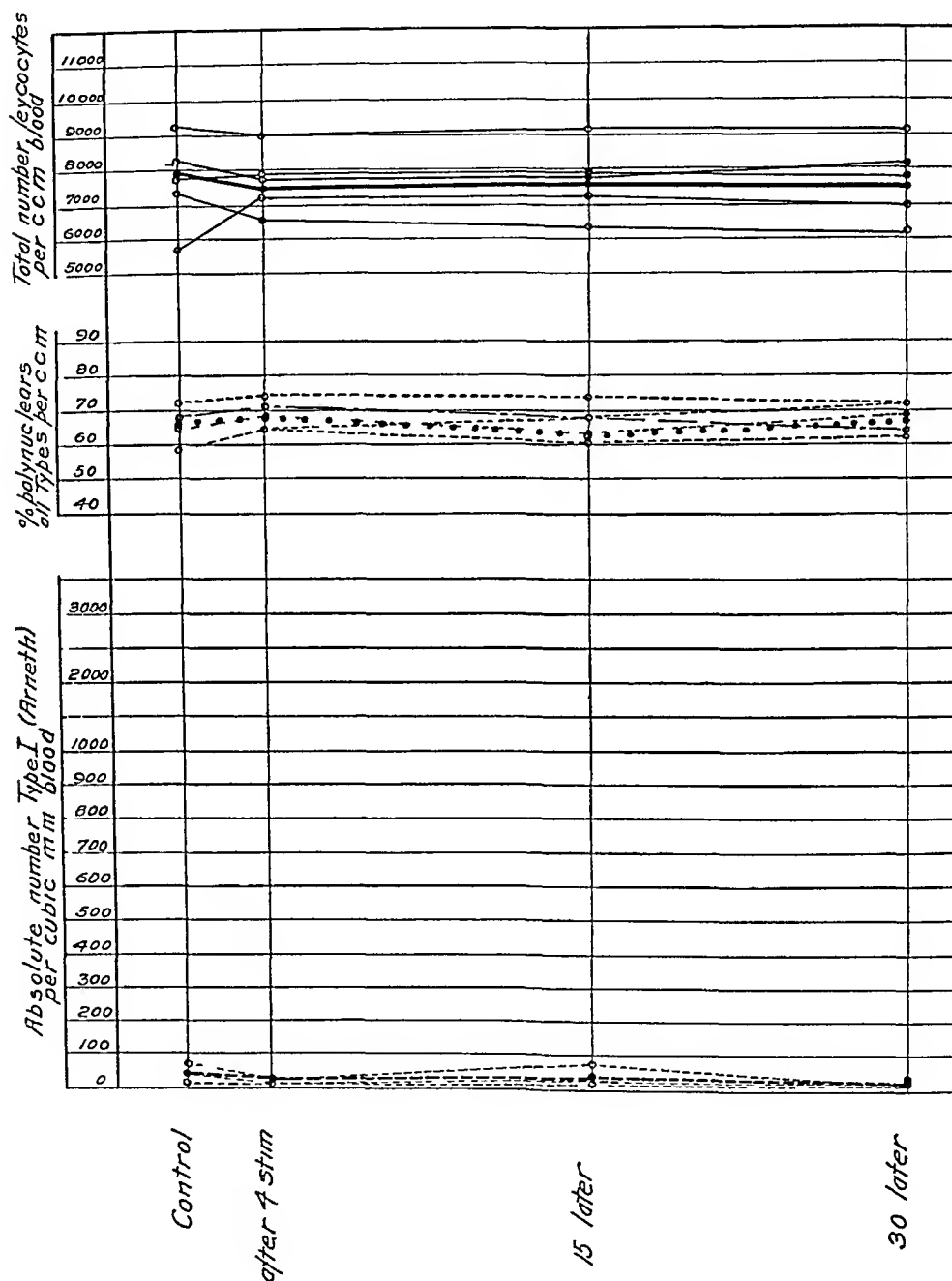


FIG 4

changes in the absolute number of Type I neutrophils. There is a sharp fall in the total number of white cells and the number of Type I neutrophils immediately after stimulation and a slight rise 15 minutes later.

The weighted means of the Cooke and Ponder formulae are charted in figure 5. The line of the average weighted means of each experiment shows greatest deflection from the control in the lowest curve. There is a less marked deviation in the second and third curves. The fourth, corresponding to the weighted means taken from elderly subjects' blood, is practically

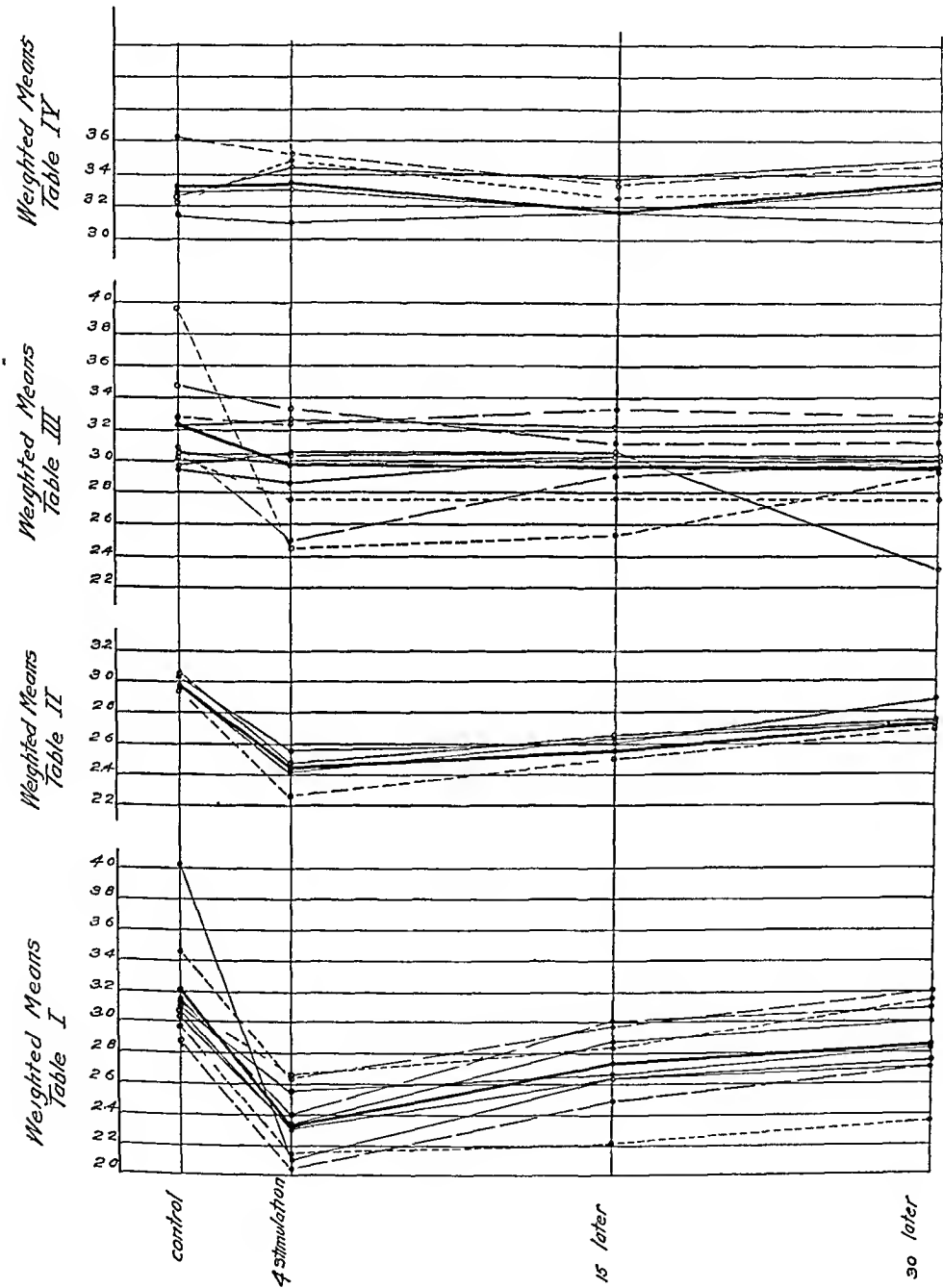


FIG 5

TABLE IV

	Total WBC	% Poly-nuclears	% Type I (Arneth)	% Type II (Arneth)	% Type III (Arneth)	% Type IV (Arneth)	% Type V (Arneth)	% Large Lymph	% Small Lymph	% Mono-cytes	% Transi-tionals	% Baso-philes	% Eosino-philes	Absolute No. Type I per cu mm
Pt 1 Control	6850	72.4	0.0	7.4	48.0	14.0	3.0	4.0	21.0	2.0	0.6	0.0	0.0	0
4' Stimulation	7200	73.1	0.0	6.8	48.2	16.0	2.1	3.8	20.0	1.5	0.6	0.0	0.0	4
15' Later	7300	73.1	0.0	7.1	47.8	15.6	2.6	4.0	21.0	1.5	0.2	0.0	0.0	0
30' Later	7000	71.7	0.8	8.2	46.5	14.2	2.0	3.6	22.0	2.0	0.5	0.0	0.2	6
Pt 2 Control	8200	68.8	0.8	8.0	36.0	20.0	4.0	2.2	26.5	1.5	0.0	0.0	1.0	7
4' Stimulation	7800	70.7	0.5	6.8	38.0	22.0	3.4	1.8	26.0	1.0	0.5	0.0	0.0	4
15' Later	7850	68.4	1.2	9.4	36.0	19.0	2.8	2.0	28.0	1.5	0.0	0.0	0.1	84
30' Later	8100	71.1	0.6	4.2	39.0	23.5	3.8	1.0	27.0	0.5	0.0	0.0	0.4	5
Pt 3 Control	9400	59.0	1.4	6.8	29.6	18.0	3.2	4.0	27.0	4.6	5.1	0.3	0.0	13
4' Stimulation	9000	65.6	0.6	4.3	32.8	21.5	6.4	3.8	28.0	1.6	1.0	0.0	0.0	5
15' Later	9200	68.6	1.0	5.0	34.0	23.0	5.0	4.2	25.0	2.0	0.8	0.0	0.0	9
30' Later	9200	64.2	1.2	6.0	34.5	22.5	4.0	4.0	28.0	2.0	1.8	0.0	0.0	11
Pt 4 Control	7400	66.4	0.8	4.5	30.5	24.6	6.0	3.0	25.0	3.0	2.0	0.0	0.6	60
4' Stimulation	6600	68.3	0.0	3.8	31.0	26.0	7.5	4.0	28.0	3.5	3.5	0.0	1.4	0
15' Later	6400	63.0	1.6	6.2	27.0	23.4	4.8	3.6	27.6	4.0	1.5	0.0	0.3	10
30' Later	6200	69.0	1.2	5.4	30.0	26.0	6.4	4.2	25.8	1.0	0.0	0.0	0.0	7
Pt 5 Control	7800	58.9	2.5	8.8	24.8	18.6	4.2	5.0	31.5	3.0	1.0	0.0	0.6	18
4' Stimulation	7850	65.3	1.8	6.5	31.0	20.0	6.0	4.5	30.0	0.2	0.0	0.0	0.0	14
15' Later	7900	61.8	2.2	7.6	27.0	20.0	5.0	5.5	29.0	2.0	1.0	0.0	0.7	17
30' Later	7800	62.6	2.4	8.0	26.0	20.0	6.2	4.8	27.0	3.0	1.0	0.0	0.8	19
Average Control	7930	65.1	0.9	7.1	33.8	19.0	4.1							20
4' Stimulation	7690	68.6	0.6	5.6	36.2	21.1	5.1							5
15' Later	7730	62.9	1.2	7.1	34.3	20.2	4.0							24
30' Later	7660	67.7	1.4	6.3	35.2	21.4	4.5							8

flat Induction current stimulation appears to be the most efficient means of deviating the index to the left in young people

DISCUSSION

By means of induction current and mechanical vibration, the normal neutrophilic formula can be quickly altered. This change is identical to the "shift to the left" which has been reported in severe infectious diseases. An important difference, however, is that there were no basophilic granules in the cytoplasm of the neutrophils of any type before or after the shift had occurred. By means of Jenner-Giemsa staining, Kugel and Rosenthal⁵ have studied the blood smears of people who had not only a marked "shift to the left" but also a preponderance of basophilic granular neutrophils in infections with poor prognoses. In our experiments, the "shift to the left" was prominent, but we failed to detect the signs of cytoplasmic degeneration with unfavorable prognoses as reported by the above authors. Furthermore, the alteration of the hemograms by our experimental procedure failed to elicit symptoms or signs of a physical abnormality in any subject.

The mechanism of this "shift to the left" cannot be explained at this time. A similar alteration of the hemogram has been produced by others using chemical and physical agents. Kennedy and Thompson⁶ have produced a "shift to the left" in the Arneth index of animals irradiated with ultra-violet light. A similar change was obtained by the feeding of irradiated ergosterol to rabbits.⁷ Danzer⁸ has demonstrated that the destruction

and absorption of tissue in vivo is followed by a deflection of the Arneth index. He has suggested that the continual and normal breakdown of body tissue provides a stimulus for the normal output of neutrophils by the bone marrow.

Study of the above tables reveals an immediate loss of the older neutrophils after induction current or mechanical vibratory stimulation. Destruction of these older cells liberates nucleic acid and its derivatives which have a definite effect on the myeloid foci.⁹

The adenine sulphate content of the blood before and after stimulation is at present being analyzed in this laboratory. From the evidence to date, there is no relationship between the "shift to the left" and the nucleotide content.

CONCLUSIONS

1 The proportion of young to old neutrophils in the peripheral blood may be reversed by induction current and vibratory stimulation of the extremities.

2 The "shift to the left" is only a temporary phenomenon in this experimental procedure, but it may be retained for several days by repeated stimulation without detrimental effects.

3 Basophilic granular degeneration of the neutrophilic cytoplasm does not occur with this "shift to the left."

4 "Shift to the left" by itself is not exclusively a sign of severe infection.

5 The production or distribution of young neutrophils is markedly decreased in senile conditions.

BIBLIOGRAPHY

- 1 CHILLINGWORTH, F. P., HEALY, J. C., and HASKINS, F. E. Reflex eosinophilia, *Jr Lab and Clin Med*, 1934, xix, 486-494.
- 2 ARNETH, J. *Die qualitative Blutlehre*, 4th ed., 1920, Leipzig.
- 3 COOKE, W. E., and PONDER, E. *The polynuclear count*, 1927, Chas. Griffin and Co., Ltd., London.
- 4 SCHILLING, V. *The blood picture and its clinical significance*, Am. ed., 1929, C. V. Mosby Co., St. Louis.
- 5 KUGEL, M. A., and ROSENTHAL, N. Pathologic changes occurring in polymorphonuclear leukocytes during the progress of infections, *Am Jr Med Sci*, 1932, clxxxiii, 657-667.
- 6 KENNEDY, W. P., and THOMPSON, W. A. R. Studies on Arneth count, deflection of count by ultra-violet rays, *Quart Jr Exper Physiol*, 1927, xviii, 263-266.
- 7 CLIMENKO, D. R. Studies on the Arneth count. XVI. The deflection of the count by irradiated ergosterol, *Quart Jr Exper Physiol*, 1930, xx, 193-199.
- 8 DANZER, M. Studies on the Arneth count. XV. The effect of tissue injury, *Quart Jr Exper Physiol*, 1930, xx, 141-147.
- 9 DOAN, C. A., ZERFAS, L. G., WARREN, S., and AMES, O. A study of the mechanism of nucleotide-induced leukopenic and leukocytic states, *Jr Exper Med*, 1928, xlvii, 403-435.

A STUDY OF 118 READMISSIONS TO OAKHURST SANATORIUM OF GRAYS HARBOR COUNTY, WASHINGTON

By HOWARD L. HULL,† M D , F A C P , *Yakima, Washington*

EVERY tuberculosis sanatorium, especially if it is tax supported, has its more or less large quota of readmissions, and yet one does not often see in medical literature studies of such statistics with efforts to account for relapses or other conditions requiring readmission. A careful consideration of such data by the staff of each sanatorium should yield valuable information and in time might help to correct some of the inherent difficulties.

The present statistics relate to Oakhurst Sanatorium at Elma, Grays Harbor County in the State of Washington. The institution is owned and maintained by the county which has an area of 1869 square miles and a population of about 60,000. It accepts only patients who have resided in the county for one year.

The data analyzed cover a period of 12 years and 9 months, from the opening of the institution in August 1921 with 22 beds, to May 31, 1934 when there were 68 beds. The records of non-tuberculous patients have been excluded from the study and also cases of the childhood type of tuberculosis because, in the latter instance, some of the earlier diagnoses would not agree with the present conception of that type of the disease. No apology is offered for the few cases presented. They represent a problem that must be met in many small institutions throughout the country where the staff is very limited and where there are not the facilities or equipment of the large well organized sanatorium, to say nothing of the extensive follow-up system so necessary for supervision of the discharged patient.

The writer, as medical director of the sanatorium, had in effect a definite program of education of the patient which began with his admission and continued throughout his stay. This was carried out by a course of reading of books on tuberculosis written especially for the laity and it was constantly supplemented by talks by the physician and the chief nurse. The patient was encouraged to ask questions regarding the general subject of tuberculosis and especially about his own condition. Except in the case of those gravely ill with tuberculosis, it is essential that the patient be given some insight into his condition in order that he may make his plans accordingly.

On the occasion of the first examination, considerable time was taken to discuss the patient's condition with him. He was told enough of the findings (physical and roentgen-ray) so that he might get an understanding of what was to be expected. It is always a problem to decide how much to tell the patient lest he overestimate his condition on the one hand or under-

* Received for publication November 15, 1934

† Formerly Medical Director of Oakhurst Sanatorium

rate it on the other. It seems obviously wrong to tell him too many details and to be too confident in venturing a prognosis. A compromise must be sought in each case.

At the time that the patient was started on the more active exercise phase of his treatment a more intensive educational program was pursued. He was encouraged to assume more and more responsibility in his own care so that at the time of his discharge he was virtually on his own responsibility. At the same time, the relatives and friends were interviewed by the physician and the patient's condition carefully reviewed and a plan of living at home outlined. It was clearly set forth just what the patient might do and what he ought not to do. Emphasis was placed upon the fact that the appearance of health and splendid physique did not justify a rapid return to former pursuits and occupation. The patient's first month at home was so planned that he would not be taking nearly as much exercise as he was taking at the sanatorium. He was warned to avoid fatigue and to endeavor to keep away from those affected with transmissible diseases, especially infections of the upper respiratory tract. He was cautioned against the use of alcohol and dissipation of any kind and advised not to return to smoking. Long trips, especially by automobile, and late hours were forbidden. He was given an appointment to return for examination in approximately one month after discharge.

Each patient on discharge was given a mimeographed sheet of instructions. He was reminded not to pay attention to the opinions of friends and relatives about his condition and what he should do. He was urged to write or to telephone to the sanatorium when in doubt.

As an addendum to this study a brief review will be given showing in a period of four years how well patients responded to the request to return for reexamination.

The statistics to be presented concern 118 discharged patients who required readmission one to four times during the period previously mentioned (August 1921 to May 31, 1934).

TABLE I

Length of Stay in Sanatorium	1st Readm	2nd Readm	3rd Readm	4th Readm
Less than 1 mo	5			
1-2 mo	15	3		
3-5 mo	29	7	3	1
6-8 mo	15	5	1	
9-11 mo	5	4	3	
12-14 mo	7	2	1	
15-17 mo	3	2		
18-20 mo	1			
21-23 mo	0			
24-26 mo	2			
36-38 mo	1	1		1
48 mo	1			
	<hr/> 84	<hr/> 24	<hr/> 8	<hr/> 2

In table 1 is shown the number readmitted and how long they stayed. For example, reading across, it is noted that of the patients who remained in the sanatorium three to five months, 29 were readmitted once, seven readmitted twice, three a third time, and one a fourth time. Further study of the table suggests that the longer a patient remained in the sanatorium the first time he was admitted, the less likely was he to have to be readmitted, and that after one readmission, the necessity for readmission became less. This is just as one would expect but it is frequently overlooked or forgotten when patients are considered ready for discharge. Often the physician's judgment is hampered by the intense desire that the patient has to go home. The mental condition of some patients is such that after a period of residence in a sanatorium they become restless and, in some instances, so homesick that they fail to give cooperation and if not discharged they either leave against medical advice or else adversely influence their fellow patients and, for the good of the institution, must be sent home.

Most sanatorium physicians are wont to urge an increase in residence in the institution to cover a long period after all symptoms and signs of active disease have disappeared as well as roentgen-ray evidence confirmatory of the same. Especially is this so if living conditions at home are poor and the patient has had a severe tuberculous infection or a low immunity. The limited bed capacity in public institutions where there is usually a long waiting list, and the financial limitations of the patient in a private sanatorium make this problem very difficult of solution and often it really leaves no choice to the medical superintendent when the situation arises.

TABLE II
Time Out of Sanatorium before Readmission

	1st Readm	2nd Readm	3rd Readm	4th Readm
Less than 1 mo	10	5		
1-2 mo	21	9	4	1
3-5 mo	12	5	1	1
6-8 mo	8	2	1	
9-11 mo	6			
12-14 mo	9	1	1	
15-17 mo	2			
18-20 mo	3			
21-23 mo	1			
24-26 mo	2	1	1	
30-32	2			
4 years	1			
5 years	2	1		
6 years	1			
7 years	1			
	<hr/> 84	<hr/> 24	<hr/> 8	<hr/> 2

The interpretation of table 2, reading across, for example, signifies that of patients who were out of the sanatorium less than two months, 10 were readmitted once, and five were readmitted twice. Most of those readmitted who were out of the sanatorium less than a month had left against medical advice or because of some emergency alleged to exist at home requiring their

presence Sanatorium physicians are familiar with the type of patient who has been admitted with the idea that he would have to stay only a few weeks. His attending physician or his family may have told him this in order to get him to consent to hospitalization. He resents the apparent deception by refusing to stay. After he has returned home he becomes worse or he realizes his mistake and often wishes to be readmitted.

Sixty-nine patients had to be readmitted within five months of discharge, most of them within two months. This table would suggest that if the patient maintains himself well during the first six months out of the sanatorium, he stands an increasingly good chance of remaining well. The few relapses that occurred at four to seven years after admission were due largely to mechanical injuries of the chest, pregnancy or severe intercurrent chest infections such as pneumonia, influenza, etc.

TABLE III
Apparent Reason Requiring Readmission

1	Retrogression	12
2	Poor home conditions	20
3	Unavoidable (86 cases)	
	<i>a</i> Extension of infection to other lung or reactivation of original site	24
	<i>b</i> Pleuritis (without effusion)	3
	<i>c</i> Pleuritis with effusion	3
	<i>d</i> Thoracoplasty	24
	<i>e</i> Convalescence from laparotomy for tuberculous peritonitis	7
	<i>f</i> Tuberculous empyema	3
	<i>g</i> Tuberculous osteitis	4
	<i>h</i> Tuberculous laryngitis	1
	<i>i</i> Tuberculous kidney	1
	<i>j</i> Tuberculous enteritis	1
	<i>k</i> Operation for non-tuberculous conditions (duodenal ulcer, sinusitis, etc.)	4
	<i>l</i> Hemoptysis	8
	<i>m</i> Influenza	2
	<i>n</i> Pregnancy	1
		<hr/> 118

In table 3, by a careful review of each history, an effort has been made to determine the probable or apparent cause requiring readmission. Under "Retrogression" were included conditions for which the patient was largely responsible such as disregard of advice as to the proper mode of living (which might include carelessness as well as ignorance), over-exercise, alcoholic debauch and other forms of dissipation. It is surprising that so comparatively few come under this heading, there being only 12 (10 per cent). In two cases, influenza was believed responsible for reactivation of inactive disease and pregnancy was thought responsible for one case. "Poor home conditions" include poor housing with many steps to climb, over-crowding, deficient ventilation and light. It also includes the case of the housewife with a large family dependent on her. Twenty (17 per cent) were so classified.

The majority of those who had to be readmitted seemed to be victims of unavoidable conditions variously classified and not apparently due to the

fault of anyone Thirty-one (36 per cent) of these were readmitted to convalesce from thoracoplastic operations or from laparotomy at which tuberculous peritonitis had been discovered

In our series only eight cases (6.7 per cent) returned because of hemoptysis In 16 instances (13.5 per cent) tuberculous complications of pulmonary tuberculosis required readmission Evidently, in 86 (74.5 per cent) it was through no fault of the patient that he had to return to the sanatorium

TABLE IV

Occupation

Nurse	1	Tile setter	1
Stenographer	3	Logger	9
Telephone operator	1	Carpenter	1
Teacher	3	Dancer	1
Housewife	40	Box factory worker	1
Common laborer	20	Abstractor	3
Student	19	Assistant postmaster	1
Laundry worker	1	Bricklayer	1
Barber	1	No occupation	10
			<hr/>
			118

TABLE V

Social Condition and Sex

Single	41	Male	40
Married	60	Female	78
Divorced	11		
Widowed	2		
Separated	4		
	<hr/>		
	118		118

TABLE VI

Nationality

American	92
Swedish	3
Norwegian	1
Australian	3
Canadian	3
Finnish	10
Italian	1
Croatian	1
Scotch	1
Greek	1
American Indian	1
Welsh	1
	<hr/>
	118

As to occupation, the housewife represented the larger group (40, or 33 per cent) It is difficult for the housewife to return to her home and maintain her good condition especially where there are small children or where relatives and friends interfere with her continuing to follow advice given on discharge It is probable that statistics of other sanatoria would show likewise the greater frequency of relapse among housewives than

among other occupations. The same is shown in the tabulation of social condition and sex where 41 (34.7 per cent) were single and 40 (33.9 per cent) were male, while 60 (50.8 per cent) were married and 78 (66.1 per cent) were female. In this series one may conclude that females, especially if married, are more likely to require readmission than are males.

Nationality seems to have no special significance in this county where the population is predominantly American born. No attempt was made to analyze further to determine how many "Americans" were of foreign parentage. American Indian patients were almost invariably sent to federal sanatoria so that only one appears on the list.

TABLE VII

Age

6 to 8 years	1
9 to 11 "	4
12 to 14 "	5
15 to 17 "	5
18 to 20 "	10
21 to 23 "	15
24 to 26 "	20
27 to 29 "	22
30 to 32 "	10
33 to 35 "	6
36 to 38 "	3
39 to 41 "	6
42 to 44 "	6
45 to 47 "	1
48 to 50 "	3
66 to 68 "	1
	<hr/>
	118

No patients under six years are admitted to this institution. In table 7, and more especially in chart 1, it is clearly shown that the age period between 18 and 32 years inclusive, comprising 77 patients (65.2 per cent), compares well with mortality statistics for tuberculosis, indicating this period to be the most dangerous for relapse or for conditions requiring readmission.

TABLE VIII

Condition on Final Discharge

Quiescent	55
Apparently arrested	7
Active	29
Dead	27
	<hr/>
	118

One of the surprising findings is that 29 or 24.5 per cent were discharged as "active." One of the aims of sanatorium care is and should be to discharge the patient at least in the quiescent stage. Of these 29, 24 left against medical advice or by their own request and their treatment obviously had not been completed. In other instances there were active tu-

CHART I

Age

Yrs 6-8 9-11 12-14 15-17 18-20 21-23 24-26 27-29 30-32 33-35 36-38 39-41 42-44 45-47 48-50 66-68



berculous patients outside the institution that urgently required admission. With crowded conditions in the sanatorium, the only possible procedure was to discharge such patients, who, though still "active," were thought capable of maintaining themselves at home, where their home conditions were believed to be satisfactory. In each instance only cases with negative sputum were discharged.

There were 27 deaths (22 per cent) which is a high mortality, but this high rate is not uncommon in public institutions where patients in all stages of tuberculosis must be accepted.

POST-SANATORIUM FOLLOW-UP WORK

At the time of his discharge the patient was given a date to report at the county clinic nearest his home. Emphasis was placed on the importance of keeping the appointment and the necessity of periodic examination and observation until told that he need not report any more. As a general rule the discharged patient was directed to report within a month and thereafter at monthly intervals until a longer period seemed justifiable. Our aim was to follow each patient for at least two years, ordering chest roentgen-ray films at suitable intervals and advising him as to the mode of living consistent with his condition. Table 9 shows these statistics for a period of four years.

One must conclude from the above that, once discharged, a large number of patients (24.2 per cent in this series) disregard advice as to reexamination or become careless and indifferent. A few can not cooperate because of conditions over which they have no control. The only expense to the

patient was the cost of his transportation to and from the clinic, so financial reasons may be dismissed. Only 10 per cent of our cases continued to report until discharged from further supervision.

TABLE IX

Discharged Sanatorium Patients and Reexaminations

Period September 1926 to September 1930 inclusive

Total discharged during period	438
Did not return to clinic for any examination	106 (24.2%)
Returned to clinic for only one examination	35 (8%)
Returned to clinic for 2 to 6 examinations	243 (57.7%)
Returned to clinic until discharged	54 (10%)

The county nurse having so large a territory to cover, was unable to visit the discharged patient as often as could be desired, this might have been a factor, as home supervision can do much to follow up and impress the advice given at the sanatorium.

SUMMARY

1 Statistics are presented from Oakhurst Sanatorium, a small tuberculosis institution owned by Grays Harbor County, Washington State, concerning 118 discharged patients who required readmission once or oftener. The period covers 12 years and 9 months (August 1921 to May 1934 inclusive).

2 The education of the patient concerning tuberculosis in general, the status of his own infection and the particular care he requires is described as a routine measure in this institution. Every possible effort is made to see that he understands his condition and the proper mode of living before discharge.

3 The statistics concern length of stay in the sanatorium before discharge and the number of readmissions required, the time out of the institution before readmission, apparent cause requiring readmission, occupation, social condition, nationality, sex and age, condition on final discharge.

4 In only 10 per cent of those readmitted did the study seem to indicate that it was their own fault. In 17 per cent poor home environment and in 74.5 per cent unavoidable conditions required readmission.

5 Brief statistics are offered relating to discharged patients and their reexaminations showing how few will continue to report at the clinics in spite of efforts to get them to do so.

CONCLUSIONS

1 Education of the sanatorium patient concerning tuberculosis and his own particular infection must be emphasized, but it is not sufficient to prevent the necessity of readmission (10 per cent in this series).

2 Too short a stay in the sanatorium is a large factor in requiring readmission. The longer the patient remains in the institution the less likely

is the necessity of his readmission because of reactivation of the disease or tuberculous complications. More beds for convalescent or "exercise cases" should be available in each institution and a longer period of observation should be possible, under fairly strenuous living conditions, before discharge.

3 The married female required readmission more than the single male or female.

4 The age period between 18 and 32 years is that in which most readmissions are necessary. This corresponds with the mortality curve for tuberculosis.

5 Leaving the institution against medical advice accounted for 25 per cent of readmissions. In the remaining cases the cause was considered unavoidable.

6 More adequate follow-up work after discharge is necessary but with financial limitations, especially in the smaller institutions, it is difficult if not impossible to carry out.

The writer acknowledges gratefully the assistance of Miss Evelyn Mason, R. N., who prepared the statistics in this article.

MYASTHENIA GRAVIS *

(SIXTH REPORT)

By WALTER M. BOOTHBY, M D , F A C P , *Rochester, Minnesota*

IN previous articles on myasthenia gravis³⁻⁶ I described in detail the classical picture of the disease and the results of treatment with glycine and ephedrine. In this paper I shall present some of the other features of the disease,[†] and will include in the bibliography a few of the more important recent articles on the subject.

As all are aware, the mortality of myasthenia gravis has been considered to be high. Goldstein, in Oppenheim's textbook, reported, without any details, 26 deaths in 38 cases, this is a mortality of approximately 70 per cent. However, Goldstein himself saw only a few of these patients, and the rest of the cases he obtained from available reports in the literature. The patients, therefore, did not have the advantage of treatment by any systematic program which would minimize the severity or the associated complications, especially those of dehydration and inanition, attributable to inability to swallow, as a consequence of involvement of the muscles of deglutition.

In the past three years 65 patients afflicted with myasthenia gravis have been seen at The Mayo Clinic. In all these cases the diagnosis of myasthenia gravis was made by consultants of the Division of Medicine and was confirmed by those of the Section on Neurology. Of these 65 patients, 13 have died. Four of the deaths can be excluded from consideration concerning the effect of treatment, because one patient committed suicide, two abandoned treatment, and one died within 48 hours of coming under observation. Fifteen of the patients are now able to carry on practically full time work and are entirely self-supporting. Twenty-five are able to do part time or light work, while only five are at present limited to a life in bed or in a chair. The remaining 12 are able to be up and about their homes and to do varying amounts of small chores.

In spite of unsatisfactory information as to the mortality among untreated patients who have myasthenia gravis, and in spite of the well known frequency of major remissions in the severity of this disease, I am confident that the mortality has been greatly reduced and that the number of patients who can be maintained at either full, or part time, work has been increased. A very severe and serious disease, of long duration, remains to be contended with, one in which many problems remain to be solved. Before there can be ground for reasonable hope of further material improvement in treatment

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

From the Section on Clinical Metabolism, The Mayo Clinic, Rochester, Minnesota.

† Motion pictures were shown after reading of the paper to illustrate the characteristic fatigability and effect of treatment thereon.

of the disease, investigators must either know, or at least have a very probable idea, not only of its metabolic disturbances but also of its etiology

In my laboratory, we have been interested in the first of these two problems, and have been investigating the metabolic abnormalities of the disease. In conjunction with Dr Adams and Dr Power we have found that in the acute stage of the disease there is a definite, negative nitrogen balance, a melting away, as you might call it, of body protein, presumably in part muscle protein. On the other hand, after the acute stage is passed there is no longer a negative nitrogen balance, and of course among those patients who are rapidly gaining in weight and strength, subsequent to their reduced stage, following the acute period, there must be a corresponding re-accumulation of protein reserve. On the other hand, marked creatinuria was observed in only six of 28 cases of myasthenia gravis, and in 22 cases the amount of creatine nitrogen excreted was less than 0.04 gm daily, and many of the patients in the latter group excreted only questionable traces of creatine. The administration of glycine always produced an increase in creatinuria, if it was previously present, and caused a small amount of creatine to appear if it were previously absent. However, a similar reaction was found to occur among normal or practically normal individuals following administration of glycine, therefore, the development of creatinuria following administration of glycine is not limited to any one disease. In fact, the largest increases attributable to glycine were found in cases of progressive muscular dystrophy, in which as is well known, a large percentage of the total creatinine nitrogen is excreted as creatine nitrogen.

In our attempt to find out whether or not the beneficial effects of glycine in decreasing the fatigability of patients who have myasthenia gravis, which we were able to demonstrate repeatedly, was specific for this disease, we administered glycine to a large number of control subjects, some of whom complained of slight or moderate fatigability, such as is so often exemplified by patients who are frequently classified (for lack of a better diagnosis) as being affected with chronic exhaustion. Many of these control subjects likewise experienced a definite decrease in fatigability, and we were therefore forced to conclude that the action of glycine was not specific for the fatigability of myasthenia gravis but had a more general favorable effect on a larger group of cases of nonspecific fatigability. There was, however, one important difference in the action of glycine on the patients who were troubled with the fatigability associated with simple chronic exhaustion from that which it had on patients who had the profound fatigability of myasthenia gravis, the former required only small doses of glycine, often not exceeding 1 gm or less three times daily, to produce a beneficial effect, whereas most patients who had myasthenia gravis frequently needed 5 gm three to six times daily. In fact, with few exceptions, none of the control group of subjects could tolerate the large doses of glycine required by patients who had myasthenia gravis except patients who had progressive muscular dystrophy. The use of glycine in asthenia has a tendency to re-

heve fatigue, but investigation has not been carried far enough to warrant any definite conclusions as to its range of therapeutic value in the various asthenic states

The chemical investigations we have pursued in regard to the cause of the beneficial effect of ephedrine in myasthenia gravis, unfortunately have given entirely negative results. Clinically, we have found, however, that large doses of ephedrine frequently can cause harmful effects when continued indefinitely, and that only the small doses of ephedrine of the order of $\frac{1}{8}$ grain or even $\frac{1}{16}$ grain, three to five times daily, as a rule can be taken with advantage over prolonged periods. We have not yet had an opportunity to investigate the metabolic effects, if any, of the action of physostigmine and prostigmine which Walker has found of immediate but temporary benefit in cases of myasthenia gravis. The reports of Walker, of Pritchard, of Denny-Brown and of Hubble in the "Lancet" indicate that these drugs, especially prostigmine, cause immediate and marked improvement of patients who have myasthenia gravis. However, they point out that these good effects last only a few hours, and that they are then followed by a period of depression. We have confirmed these clinical observations and, like the investigators named, have been unable as yet to find a method of continued administration which will often cause a consistent improvement such as we have found following the use of glycine, both with and without ephedrine.

As regards the etiology of myasthenia gravis, we have cooperated with Dr. Rosenow in attempting to determine whether or not the toxic factor in myasthenia gravis possibly can be of microbic origin. There are phases of the disease which suggest that such may be the case. First, we reviewed the past histories in the available cases and in our third report⁴ stated that 35 per cent of our patients (at that time we had had 20 cases) could definitely ascribe the onset of the disease to a more or less severe infection of the upper part of the respiratory tract and the subsequent patients have given similar suggestive evidence. Second, as a result of careful pathologic and histologic studies made by Dr. Robertson, on the material obtained at necropsy of subjects who had had this disease, it appeared possible to him, from the appearance of the microscopic sections of the muscles, that the lymphocytic infiltration and degeneration found might be the result of an infectious process. Dr. Butt, in Robertson's laboratory, has been able to demonstrate streptococci in some of the muscles obtained at necropsy of subjects who had had myasthenia gravis. These studies are still in progress, and we are not yet prepared to do more than state that we consider it advisable to extend them. As such an investigation including the necessary control studies takes time to complete, we have tried clinically, in a few cases, the effect of the use of an autogenous vaccine prepared by Dr. Rosenow from cultures obtained from the throats of patients, because such cultures frequently produce a condition in rabbits and in monkeys that simulates the fatigability seen in cases of myasthenia gravis. While our efforts to determine the etiology of myasthenia gravis are as yet inconclusive, they are

of sufficient interest to encourage us to continue these lines of investigation

From this brief digression, I must now return to a very practical matter, namely, the early recognition of this disease, in order that the development of its serious manifestations may be prevented, at least in part

In myasthenia gravis, almost invariably the first muscle groups to show evidence of increased fatigability are the extrinsic muscles of the eyes which are concerned with focusing, and the fatigability becomes manifest to the patient by transient blurring of the vision and later, actual diplopia. The first symptom usually evident to the patient's family is drooping, or ptosis, of the upper eyelid, especially in the afternoon or evening, after fatigue. In the early stages of the disease these phenomena usually are very transient, and disappear entirely after rest. Somewhat later, or possibly simultaneously, the patient notices that he fatigues easily on talking, especially on strenuous vocalization, as from public speaking or reading. Articulation of long words becomes difficult and as a result the patient's speech sounds thick and indistinct. If, after fatiguing the laryngeal and pharyngeal group of muscles by talking, he attempts to drink liquids or eat solid food, he has serious difficulty in swallowing. Liquid may be regurgitated through the nose, the patient simply has not the strength to masticate solid food, and if he attempts to swallow it he does not succeed and may be thrown into a violent spasm of choking and coughing which, for a few minutes, may be very distressing. After a night's rest the patient is likely to be much better, and the symptoms are apt to recur only toward the end of the day, when the excessive weakness sometimes develops very rapidly. In some cases, after a few weeks of such symptoms, accompanied by a feeling of general lassitude not at that time usually described as actual fatigue, the symptoms may almost entirely disappear for weeks, months, or even years. More frequently, the weakness and lassitude spread to other groups of muscles, and the patient becomes fatigued on the slightest exertion. The muscles especially affected are those of the neck, arms, legs and back. Within six or eight weeks after the onset the patient may be so weak that he can barely turn over in bed or raise his hands to his face, he may have the greatest difficulty in swallowing and, because of fear of choking, may avoid all but the smallest amounts of foods and liquids, these he takes with manifest difficulty. Dehydration and inanition supervene, and subsequently death appears to be rapidly approaching. At this point, a surprising turn in the course of events may develop, even without treatment, and the strength of the patient gradually returns so that in a few weeks he is up and about, although very rarely in untreated cases is he sufficiently strong to work. These cycles of increased fatigability followed by improvement succeed one another at different intervals, although many patients seem prone to have a space of three or four weeks between the lower depths of depression and the higher peaks of remission, in addition, major trends are often superimposed on these minor fluctuations of shorter or longer duration. These long swings and sharp, small, daily, and more pronounced

weekly, fluctuations apparently are explainable only on the assumption of a similar variation in the intensity of the cause of the disease, as, for instance, if it is assumed that the toxin which causes the muscular fatigability is produced by variations in rate of growth of bacteria, as illustrated in tuberculosis. The disease is, however, afebrile.

One of the most distressing and annoying minor factors one has to contend with in the treatment of patients is the thick, slimy, stringy mucus, secreted apparently by the mucous membrane of the mouth and pharynx, and possibly also by the salivary glands. The amount of the mucus varies greatly from day to day, from week to week, and from month to month, whenever it is present in marked degree, the patient's general condition is usually not as good as at other times, in fact, there is often a very definite correlation between the patient's general condition and the amount of this mucus. At the times when there is much oral mucus the patient is usually unable to swallow much, if anything, and until remission occurs it is necessary to feed him by means of a catheter introduced through the nose into the stomach, to prevent the additional ill effects of dehydration and inanition.

Constipation, on the other hand, is not such a difficult condition to control, although it is a very frequent and annoying complication. Repeated enemas are necessary and strong cathartics should be avoided.

In general, there is no pain of any kind connected with the disease, nor is there any soreness or tenderness of the muscles such as there is in typical myositis. On the other hand, there is characteristic flabbiness of all of the muscles of the body, which is especially noticeable if the patient is of rather obese type. The patient cannot smile or pucker up his lips to whistle. The face is absolutely blank, and when talking to him, the physician has the feeling that the patient is completely indifferent to and even bored by the information that is being given him about his disease. This absentee or blank expression has often caused an erroneous diagnosis of a melancholic type of psychoneurosis or even of a brain tumor, and the misinterpretation of the extreme muscular fatigability as mental apathy and laziness. On the other hand, I have seen a case of myasthenia gravis in which the diagnosis, on detailed analysis, could hardly be questioned, misinterpreted because of the fact that the syndrome of myasthenia gravis was superimposed on a mild hysterical basis which the patient had displayed for years previously. There is, of course, no reason why an hysterical type of individual cannot have myasthenia gravis. Admittedly, under such conditions, distinction between the two sets of symptoms, and their correct interpretation, is very difficult.

Illustrative of the characteristic fatigability in this disease, and of the effect of treatment thereon, is the case of an eastern surgeon who has passed through a very severe attack of myasthenia gravis. Twelve months ago he was unable to turn over in bed, he could not light his own cigarette or even raise his hand to put it in his mouth, and he had to be tube-fed for months. He is now in good condition. He has returned to his surgical practice and is able to perform a good day's work. His future course, to be sure, cannot

RECENT STUDIES ON ANTI-HORMONES¹

By J B COLLIP, F A C P, *Montreal, Quebec, Canada*

ABOUT a year ago at the Chicago meeting of this Society it was my privilege to report upon a theoretical conception which I had evolved in an endeavor to explain certain results which had been obtained in our studies on pituitary extracts, and with a view to directing further work along specific lines. Tonight it is again my privilege to report to you the results which have been obtained in the McGill Biochemical Laboratories during the past year in the course of studies upon anterior pituitary physiology, but with particular reference to anti-hormones.

The anti-hormone theory as originally proposed was as follows:

For each hormone there may be an opposite or antagonistic principle. This antagonist is present in the normal subject but may not be detected until it exceeds in amount the hormone substances with which it is balanced. The analogy was drawn between the hormone-anti-hormone complex and a chemical "buffer" system, and in this way the anti-hormone theory was related to the principle of inverse response. The postulated dual hormone control of peripheral structures is analogous to the proved dual nerve control (sympathetic and parasympathetic).

The so-called anti-hormone was considered as a true hormone in every way and not as the result of an antigen-antibody response.

Before discussing this theory in the light of the results of further experimental work, I should like to refer briefly to terminology.

The term "hormone" was originally applied by Starling¹ to stimulating principles such as that contained in the duodenum after treatment with acids and the expression was later extended to include the active principles of all internal secretions. So long as only exciting agents were known there could be no objection to the extension of this term, but since agents which produce depression or cessation of function were known to exist in the body, Schafer² coined the word "chalone" to distinguish such agents which act as depressants or inhibitors from those which were excitant (hormones). A chalone was defined by Schafer as an endocrine product which inhibits or diminishes activity as distinguished from a hormone, which excites to increased activity. All internal secretions were spoken of by Schafer as "autacoids". Excitatory autacoids were the hormones and inhibiting autacoids were the chalones. In spite of the very logical nature of Schafer's objection to the use of the word "hormone" to describe all of the internal secretions both excitatory and inhibitory, the term has been accepted by general usage.

¹Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

²From the Department of Biochemistry, McGill University, Montreal.

While there may appear at first sight to be an analogy between the substances which I have called "anti-hormones" and the "chalones" of Schafer, the theoretical conception of the mechanism of production and the physiological significance of the former were such as to demand the use of a descriptive and distinguishing term

The idea of the production of a hormone-inhibitory substance which circulates in the blood stream and is able to neutralize the effects of a hormone was probably first expressed by Mobius³ In experiments on thyroidectomized sheep he found that the blood of such animals neutralizes the action of thyroid hormone Preparations of the blood of such thyroidectomized animals have been made available by the Meick factory under the name of "Antithyreordin Mobius" This preparation has been used clinically and several authors claim to have obtained good results in cases of Graves' disease The first investigator who tried to obtain a hormone-neutralizing substance using an endocrine preparation as an "antigen" was probably Blum Later he repeated Mobius' experiments and confirmed the findings on thyroidectomized animals, but at the same time he noted that thyroid hormone inhibitory substances are also present in the blood of normal sheep The name "catechin" has been given to these inhibitory substances⁴ Blum's experiments were later extended by Legiardi-Laura, who treated horses with posterior pituitary preparations and found that the serum of such animals decreased the glycosuria in many cases of diabetes⁵ He claimed also that this serum was equally effective in the treatment of hypertension⁶ The experiments of this author and of Blum are difficult to evaluate, since little is said in their original publications about the nature of the antigen used, the doses given, or other details concerning the treatment of the donor animal The experiments of Koyano⁷ in 1923 are open to the same criticism He injected beef pituitary emulsions intraperitoneally into male rabbits, and stated that the serum of such animals produces marked histological changes in the hypophysis of rats He called his preparation a "specific immune serum" In 1924 Cotte⁸ published a series of experiments in which extracts of fowl ovaries were chronically injected into male rabbits Thus a "serum anti-ovaire" was obtained This serum changed the color of the plumage in hen-feathered cocks The experiment was interpreted as a further proof of Morgan's theory concerning the "corpus luteum cell nature" of certain cells in the testes of the hen-feathered cock In the same year de Jongh⁹ observed that certain insulin preparations are less active in larger doses than in smaller ones, while very large amounts of the same preparation again show an increase in potency Mathematical considerations led the author to interpret this double-peaked curve as the result of an insulin-inhibitory substance superimposed on the usual insulin effect The name "anti-insulin" has been coined for this substance Further purification removed this anti-insulin from the original preparation Similar experiments led Nobel and Priesel¹⁰ to the assumption that anti-insulin is present in crude pancreatic extracts Meyer-Bisch and his coworkers¹¹

observed that pancreatic secretion increases the blood sugar of experimental animals, and concluded that anti-insulin is excreted into the duodenum. The primary hyperglycemia observed after the administration of crude insulin preparations has also been attributed to the presence of anti-insulin (Wichels and Lauber¹²). Sahyun and Blatherwick¹³ observed that rabbits on a high carbohydrate diet, injected chronically with insulin, become "immune" to this hormone, so that even 70 to 100 units do not elicit convulsions. The blood sugar response in such "immunized" animals is also much less than in the non-pretreated controls. The name "anti-hormone" has also been used by Wiese¹⁴. This author found that testicular extract coagulates the follicular fluid of nymphomaniac cows, but has no effect on the follicular fluid of normal animals. This phenomenon was attributed to the formation of "anti-hormones" in the nymphomaniac cow. The administration of testis extracts was found to be effective in increasing ovarian activity in cattle, and the author believed this to be due to the production of "anti-hormones".

The earlier experiments of Blum on "catechin" have aroused particular interest because of the good clinical results which many investigators were able to obtain with these preparations. Numerous publications have appeared more recently on similar anti-thyroid hormone preparations. Thus Herzfeld and Frieder¹⁵ have prepared a catechin from blood, and this preparation is now on the market under the name of "Thyronorman". It is said to alleviate the symptoms of Graves' disease. It is interesting to note in this connection that Branovacky¹⁶ showed that the blood of patients suffering from Graves' disease increases the oxygen sensitivity of rats in the well-known Ascher experiment, and that this effect is neutralized by the administration of blood serum from myxedema patients. Asimoff¹⁷ reports that the serum of thyroidectomized sheep inhibits the metamorphosis effect of thyroid hormone in the axolotl, and Gurber and Geszner¹⁸ found that this metamorphosis-antagonizing principle is in the euglobulin fraction. Since Lewit and his coworkers¹⁹ were able to obtain similar effects with normal blood, they doubt the specific nature of such catechins. Recently, Saegesser²⁰ observed that the serum of myxedema patients neutralizes thyroxin in Reid-Hunt's acetonitril test—a finding which reminds one of Branovacky's experiments concerning the decrease in oxygen sensitivity which we discussed above. Saegesser states that his anti-thyroid substance is lipid-soluble, and since he also observed that cholesterol exerts a similar effect he considers it possible that this action is a simple chemical antagonism.

This discussion on the historical development of our ideas on the production of hormone-antagonizing substances would not be complete without mentioning that thyro-globulin-antagonizing substances have been obtained by the administration of thyroglobulin,^{21, 22, 23} and that specific anti-ferments have been produced and demonstrated in the blood of experimental animals chronically treated with extracts of endocrine glands by Abderhalden, who called such ferments "Abwehrfermente".

The hormone-antihormone theory was proposed (1) as a possible ex-

planation of certain experimental results obtained in our laboratory, (2) and more important, as a guide to further work. Whether this theory is representative of an actual physiological mechanism will appear with the passage of time, and in the light of the results of the further work. Since this theory was put forward, a year has passed. Such a period is not long, but intensive work done in this field both by my collaborators at McGill and independent workers in other laboratories has strengthened my belief in the reasonableness and the validity of the theory as a sound working hypothesis.

Our own work has shown that specific antagonistic substances (anti-hormones) for the thyreotropic, ketogenic and maturity principles of the anterior pituitary can be demonstrated in the blood of animals treated with extracts containing these principles, and that similar specific antagonistic substances may occur spontaneously in the blood of certain patients*. A specific antagonistic substance for the anterior pituitary-like hormone of human placenta and pregnancy urine has also been demonstrated.

Although Loeb²⁴ has been unable to obtain evidence of an inhibitory substance for the thyroid-stimulating principle in guinea pigs treated with this principle until they had become resistant to it, others^{25, 26, 27, 28} have confirmed our results relative to the demonstration of inhibitory principles in the blood of animals treated for long periods with certain hormone preparations.

Rogowitch²⁹ noted enlargement of the pituitary of dogs and rabbits following thyroidectomy. Since that time as a result of the pioneer work of Adler,³⁰ Allen,³¹ Smith and Smith,³² and Spaul³³ on tadpoles, of Uhlenhuth and Schwartzbach³⁴ on salamander larvae, of P. E. Smith,³⁵ and Foster and Smith³⁶ on rats, and of Loeb³⁷ and Aron³⁸ on guinea pigs, the interrelationship between the anterior pituitary and the thyroid has been thoroughly established. It is of interest to note here that Loeb was the first to produce hyperplasia in the thyroid of the guinea pig and to point out the possible etiological significance of the anterior lobe principle in Graves' disease. Thyroid hyperplasia has been produced in a variety of animals by treatment with anterior pituitary extracts and a number of investigators have commented upon the lack of response in animals that have been treated for varying periods of time. It was this induced state of resistance to the thyreotropic hormone that Dr. Anderson and I³⁹ made a subject of special study last year and the outcome of this work was the clear-cut demonstration that the blood of the hormone resistant animal contained a substance antagonistic to the thyreotropic hormone. The method which we have used for the detection of the anti-thyreotropic principle is as follows.

Otherwise untreated hypophysectomized animals are injected twice daily with 0.5 c.c. to 1 c.c. of the serum to be tested. On the second day injections of a standardized thyreotropic extract are started, twice daily. Control animals are treated similarly except that normal serum is used. Metabolic

*I am greatly indebted to Drs. A. D. Campbell and J. S. L. Browne for their cooperation in the selection of blood samples from patients for anti-hormone investigations.

rates are taken daily In the case of a positive test complete or nearly complete inhibition of the increase in metabolism seen in the control animals is obtained The test is quite applicable to the study of sera of patients and already we have demonstrated the antagonistic substance in the blood of 10 patients, in all of whom it has occurred spontaneously and not as a result of pituitary therapy We have of course, obtained numerous negative results with normal human sera

In general it may be said that wherever we have a specific biological test for a hormone, the same method is applicable with but slight modifications for testing for antagonistic substances One must be able, of course, to distinguish between specific inhibitory or antagonistic substances and non-specific inhibitory effects Thus in the case of insulin the existence of a specific anti-hormone substance in the sense to which I have referred has not been established Mr Black ⁴⁰ of my laboratory has been able to show, however, that the hypoglycemic reaction to insulin which has been nixed with normal or diabetic serum and incubated for one hour was greatly lessened when the mixture was injected subcutaneously, whereas the same material given intravenously showed no appreciable loss in potency Similarly, Dr Kutz has shown that rats on a high carbohydrate diet may be given increasing doses of insulin daily until 200 units a day are being administered without any hypoglycemic reaction being obtained This suggested a tolerance to insulin had been developed, but it was shown at once that control rats on the same diet were apparently unaffected by 200 units of insulin Again, in the case of the parathyroid hormone, Dr Pugsley has shown that there is non-specific inhibition of the acute effects of the hormone when it is mixed with blood serum and the mixture administered to rats in the usual manner by intraperitoneal injection No such inhibitory action of serum on the parathyroid hormone was noted when the mixture was given by intravenous injection to the dog Neither was there any inhibitory effect when serum and hormone solution were injected separately into rats, even though the serum injections were started some days ahead of the hormone

We feel that the most satisfactory, although not the simplest method of demonstrating a specific hormone inhibitory substance is that of pre-treatment of the test animals with the serum or serum extract to be tested This is followed by simultaneous injections of a standard dose of hormone and serum or serum extract Consistent inhibition of the hormone effect with the anti-hormone serum when the experiment is adequately controlled would seem to establish definite proof of the existence of the antagonistic substance in the serum tested Under some circumstances it is possible to shorten the test by mixing *in vitro* the hormone extract and the serum to be tested and then injecting the mixture This method is safe only when non-specific inhibitory effects of normal serum can be excluded No doubt a variety of satisfactory methods of studying the hormone anti-hormone relations in blood and serum or even organs will ultimately be evolved, but for the pres-

ent we are making use almost entirely of the "in vivo" method outlined above

The establishment of a state of resistance to any hormone extract as a result of long-continued injections of the extract is of itself indirect evidence of the existence in excess amounts of an antagonistic substance. Since such a resistant state may theoretically be due to a variety of causes it seems essential, in any case of an apparent hormone resistant state, that it should be shown that the "resistance" is transferable before a true hyper-antihormone condition can be stated to exist.

Anti-A P L It has been shown that continuous injection of A P L leads at first to a great increase in the size of the ovaries but this effect passes off in the course of a few weeks and the ovaries return to normal or even subnormal size in spite of the continued injections of the hormone. The seminal vesicles and prostate of males treated with A P L continuously have been shown to follow a weight curve somewhat similar to that of the ovaries of treated females⁴¹. In the light of our results with serum of thyreotropic hormone resistant animals, it was not surprising to find that the serum of animals rendered non-responsive to A P L, when injected into immature rats, completely inhibited both the estrogenic and ovarian response to this gonadotropic substance⁴². Anti-A P L serum of relatively high titre has been produced in the rabbit, and recently Dr. Carl Bachman⁴³ has shown that the antagonistic effect of this anti-substance can be demonstrated in the rabbit. Thus an isolated non-pregnant adult female rabbit was injected twice daily for two days with 0.5 c.c. of anti-A P L rabbit serum. Two hundred units of A P L were then administered and inspection 48 hours later showed that there had been complete inhibition of the normal ovarian response to A P L. The characteristic effect of A P L upon the testes, seminal vesicles and prostate of immature males has also been completely inhibited by anti-A P L serum.

Anti-A P L serum is of special interest because Dr. Bachman has been able to show that it contains a true antibody for a proteose-like substance which is a contaminant of our preparation. This true antibody can be demonstrated by complement fixation and precipitin reactions. That it is not the anti-hormone is fairly conclusively shown by the fact that the anti-proteose substance may still persist in the blood of a rabbit weeks after the serum has lost its physiological antagonistic effect upon the hormone due to cessation of A P L injections.

Anti-A P L is of interest in another way because it is, as far as we are aware, a foreign hormone to the animals which have been used to produce successfully an antagonistic serum to it.

We have had as yet no direct evidence of the presence of anti-A P L in the pregnant woman. To assume that it is present would seem on a priori grounds reasonable. At this point I cannot resist re-stating the suggestion that the fundamental disturbance in certain toxemic cases may be a hor-

monal imbalance This might involve not only A P L and anti-A P L but also true pituitary hormones and even members of the estrogenic group

Some years ago we became interested in considering the toxemias of pregnancy from the standpoint of hormonal imbalance, but we had to abandon any serious attack upon the problem because of the lack of the necessary base lines characterizing the normal The working out of these alone we saw would require enormous numbers of animals and, more important still, the development of new methods which would allow of more exact assays of the various hormones involved The recent work of Marrian and his associates,⁴⁴ for example, shows that most of the estrin assays of the past may have to be discarded because nearly all of the estrin in fresh pregnancy urine is ether insoluble, and also of very low estrogenic potency when tested on castrates In other words, estrin is in the native state combined with some as yet unknown substance which alters both its physical and physiological properties In 1930 I described a method for fractionating human placenta into three types of estrogenic extracts^{41, 45} One of these, an alcohol soluble, ether insoluble fraction was clearly differentiated from estrin as then known and from the gonadotropic substance "A P L" The active principle of the extract was characterized not only by its physical but also by its physiological properties Some of these latter showed relative ineffectiveness on castrates as compared to marked estrogenic activity on immature female rats, resistance to peptic and tryptic digestion and activity orally Later this same estrogenic substance was demonstrated in pregnancy urine and crystalline trihydroxyestrin was obtained therefrom only after vigorous hydrolysis in an autoclave had rendered the estrin of the ester ether soluble⁴⁵ Marrian's recent work has confirmed and greatly extended the significance of these earlier observations

The Anti-Maturity Factor of the Anterior Lobe It has been shown that daily implantation of fresh rat pituitary into female rats leads at first, as in the case of A P L, to ovarian enlargement⁴² After some weeks the ovaries decrease in size and although now unresponsive to implants they respond in a normal manner to A P L

Extracts of pig anterior lobe rich in the maturity factor have been administered over a period of weeks to rats By the method of pretreatment of immature females with serum obtained from maturity extract resistant rats, the presence of an antagonistic substance for the maturity principle in these sera has been clearly demonstrated

We have been able to demonstrate the presence of the anti-maturity factor in the blood serum of certain patients The clinical significance of a positive finding of the anti-maturity factor in the blood stream is not yet fully apparent The treatment of such a case with pituitary sex hormone would obviously be contraindicated

The Anti-Ketogenic Principle Hoffmann and Anselmino⁴⁶ and Magistris⁴⁷ noted an increase in the acetone bodies in the blood after the injection of anterior pituitary extracts Burn and Ling⁴⁸ found that the injection of

an alkaline extract of bovine anterior pituitary lobes greatly increased the acetoneuria of female rats kept on a filtered butter diet. Butts, Cutler and Deuel⁴⁹ obtained similar results in fasted rats of either sex. Recently Black, Collip and Thomson,⁵⁰ using both the Burn and Ling butter diet and the method of fasting of Butts, Cutler and Deuel, extended these findings and made use of these methods to study the effects of long-continued treatment with anterior lobe extracts rich in the ketogenic factor upon the acetoneuria of a high fat diet or of fasting. The method of fasting proved so satisfactory in the preliminary experiments that thereafter it was used as a routine. The results obtained in this study were quite clear-cut. The characteristic acetoneuria of fasting was practically abolished in those animals which had been made resistant to the extract by repeated injections. Also normal animals pre-treated with serum from resistant animals manifested no appreciable ketonuria when fasted and injected with a standard dose of a ketogenic extract. Mr. Black⁵¹ has shown that the ketogenic hormone resistant animals develop practically no ketosis when given massive doses of phlorhizin, in spite of the fact that the usual glycosuria was produced. The control animals had extreme ketosis and those on the larger doses died. Incidentally, I may remark that we have definite proof that the ketogenic principle is quite separate and distinct from the thyrotropic, adrenotropic and growth hormones.

Dr. Kutz has been able to demonstrate recently that pancreatectomized dogs given suitable dosage for a sufficient time of anterior pituitary extract containing the ketogenic principle, during a period in which they are being maintained in good condition by adequate insulin therapy and dietary control, may on withdrawal of insulin show no appreciable ketonuria. Such animals are in many respects similar to the "Houssay dog"—namely, the hypophysectomized-pancreatectomized animal.

The recent report by Long and Lukens⁵² of the failure of adrenalectomized-pancreatectomized cats to show ketosis even when injected with anterior pituitary extracts is of tremendous importance in relation to the physiology of the ketogenic principle, for it suggests that the latter may work as a trophic hormone on the suprarenal. Since our studies have clearly established the fact that the purified adrenotropic principle of the pituitary is non-diabetogenic in the Houssay preparation and non-ketogenic in the fasting rat, it is possible that there are two trophic hormones of the anterior pituitary acting on the suprarenal. On the other hand, Mr. Black of our laboratory has been able to obtain marked ketogenic effects with anterior pituitary extracts not only in hypophysectomized rats, in thyroidectomized rats, in thyroidectomized-hypophysectomized rats, but in adrenalectomized rats. In view of the fact that the rat may have small amounts of accessory cortical tissue, Mr. Black's positive results on adrenalectomized rats treated with ketogenic extract are not necessarily in contradiction with the negative results of Long and Lukens on the adrenalectomized cat.

Our conception of the mechanism by which the ketogenic principle

functions must of necessity remain rather vague until the results of further work enlighten us. It is, however, of great interest to note that we have evidence of the occurrence spontaneously in the blood of several patients of an anti-ketogenic principle and very recently Dr Kutz has been able to demonstrate such an anti-ketogenic substance in extracts of certain urines.

The Anti-Growth Factor We have abundant indirect evidence of an anti-growth factor. Hypophysectomized rats treated with purified growth hormone almost invariably cease to respond to it after a period of five to six weeks. Serum from such animals has antagonized the growth hormone in otherwise untreated hypophysectomized rats. Unfortunately our experiments of this type have been limited in number and a much larger series will have to be carried out before direct proof of an anti-growth principle can be said to have been definitely established. Animals treated with crude anterior lobe extracts have continued to grow for longer periods and the very interesting possibility arises that the production of anti-hormones may be greatly modified by the degree of purity of the hormone extract used in treating the experimental animals.

DISCUSSION

The experimental evidence which I have given furnishes strong support for the anti-hormone theory. I do not state that other interpretations may not be made of the results. All of the various extracts which we have used to demonstrate the production of antagonistic substance contain protein-like material, so that there was always the possibility of a true antigen-antibody response in the treated individual. We do not believe that this latter possibility affords an adequate explanation for the anti-hormone responses observed, for the following reasons:

- 1 The studies of Dr Carl Bachman on anti-A P L serum have shown that the anti-hormone effect does not parallel the anti-body content.

- 2 Rats have been made resistant to the maturity hormone of rat pituitary by continued implantations of rat pituitary.

- 3 Rats made resistant to the ketogenic principle by a long period of daily injections of an extract made from ox anterior lobes have been shown by Mr Peter Black to be equally resistant to the ketogenic extract made from sheep or pig anterior lobes.

- 4 There is spontaneous occurrence in the serum of certain individuals of a substance capable of inhibiting an anterior lobe principle. Thus positive inhibition of the maturity principle, of the thyrotropic principle, and of the ketogenic principle has been observed.

Site of Production of Anti-Hormones We are completely without direct evidence which might throw some light on the source of the antagonistic substances produced in animals treated over a long period with anterior pituitary principles. Anderson and Collip⁵¹ demonstrated the development of a refractory state to thyrotropic hormone in hypophysectomized rats.

The anti-thyreotropic substance was demonstrated in a thyroidectomized dog after several weeks of treatment with the hormone. Castrated rats and rabbits* have been successfully used to produce anti-A.P.L. sera. It would therefore appear that the target organ can be excluded as playing an essential rôle in the production of the antagonistic hormone.

On the other hand, there is some evidence that antagonistic principles may occur in the same gland. Riddle⁵⁴ has recently shown that purified prolactin is definitely antagonistic to the gonad, and we find that prolactin has a definite inhibitory effect on the action in the rat of a maturity hormone extract. Whether antagonistic effects of this type are of the same order as the anti-hormone effects cannot be stated.

In view of the fact that a somewhat extensive search for evidence of the existence of anti-hormones to estrin, to parathyroid hormone and to insulin has failed as yet to demonstrate such, it is possible that the anti-hormone theory should be applied only to trophic principles.

It must be borne in mind also that a resistant state to a certain hormone may be due to a purely local condition and not necessarily to the presence in abnormal amounts of an anti-hormone or a specific antagonistic substance. Thus it is now well established that the ovaries of the very young animal are non-responsive to anterior lobe maturity hormone. Certain hypoglandular as well as hyperglandular states may be due to decreased or increased responsiveness respectively of the gland concerned to the specific trophic principle normally influencing it.

REFERENCES

- 1 LANE-CLAYTON, J. E., and STARLING, E. H. An experimental inquiry into the factors which determine the growth and activity of the mammary glands, *Proc Roy Soc, Series B*, 1906, lxxvii, 505-522.
- 2 SCHAFER, E. S. The endocrine organs, 1924, Longmans, Green and Co., London.
- 3 MOBIUS, P. J. Die Basedowsche Krankheit, 1906, A. Holder, Wien.
- 4 BLUM, F. Über die antithyreoidalen Eigenschaften des Blutes und das zugrundeliegende Katchin, *Schweiz med Wchnschr*, 1933, lxiii, 777-781.
- 5 a LEGIARDI-LAURA, C. Antipituitary serum in arteriosclerosis and diabetes mellitus, *New York Med Jr*, 1919, cx, 713.
b LEGIARDI-LAURA, C. Antipituitary serum, a biological treatment of diabetes, *New York Med Jr*, 1923, cxvii, 594-597.
- 6 LEGIARDI-LAURA, C., and BRIN, C. J. Control of hypertension by pituitary serum, *Internat Clin*, 1929, iii, 28-33.
- 7 Koyano, T. *Mitt u d med Fak d Kais Univ Tokyo*, 1923, \\\, 363.
- 8 COTTE, J. Injection de serum anti-ovaire a un coq gvaudromorphe, *Compt rend Soc d biol*, 1924, xci, 1252-1254.
- 9 DE JONGH, S. E. *Biochem Jr*, 1924, \viii, 833.
- 10 NOBEL, E., and PRIESEL, R. Insulinversuche an Ratten, *Ztschr f d ges exper Med*, 1925, \xviii, 1-5.
- 11 MEYER-BISCH, R., BOCK, D., and WOHLFENBERG, W. *Naunyn-Schmiedeberg's Arch*, 1928, cx\\vi, 185.
- 12 WICHELS, P., and LAUBER, H. Insulin und Hyperglykämie, *Deutsch Arch f klin Med*, 1932, cl\\ii, 613-621.

- 13 SAHYUN, M, and BLATHERWICK, N R Pathological response of rabbits to insulin, Jr Biol Chem, 1928, lxxix, 443-460
- 14 WIESE, E Ein Beitrag zur Kenntnis der Geschlechtshormone, Berl tierarztl Wchnschr, 1928, xlv, 353
- 15 HERZFELD, E, and FRIEDER, A Über das Katechin (Hemmungstoff) der Schilddrüse und dessen therapeutische Verwendung bei Morbus Basedow, Deutsch med Wchnschr, 1933, lix, 84-86
- 16 BRANOVACKY, M Die Neutralisation des Blutserum von Zwergkretinen mit atrophischer Schilddrüse, Mitt a d Grenzgeb d Med u Chir, 1926, xxvix, 593-608
- 17 a ASIMOFF, G Zur biologischen Kontrolle des Antithyreokrins, Arch f d ges Physiol, 1926, ccxv, 191-196
b ASIMOFF, G Med Biol Ztschr, 1926, ii, 37
- 18 GURBER, E, and GESZNER, O Naunyn-Schmiedeberg's Arch, 1928, cxlix, 370
- 19 LEWIT, S G, BERLAND, N S, and RYWKIN, I A Die biologische Kontrolle des Antithyreoidins, Ztschr f d ges exper Med, 1930, lxxi, 506-524
- 20 SAEGERER, M Die Schutzfunktion des Organismus bei Thyreopathie, Klin Wchnschr, 1933, xii, 672
- 21 HICKS, C S Innervation and secretory path of thyroid gland, Jr Physiol, 1926, lxii, 198-202
- 22 a HEKTOEN, L, and SCHULHOF, K Precipitin reaction of thyroglobulin, Jr Am Med Assoc, 1923, lxxx, 386-387
b HEKTOEN, L, FOX, H, and SCHULHOF, K Specificness in precipitin reaction of thyroglobulin, Jr Infect Dis, 1927, xl, 641-646
c HEKTOEN, L, CARLSON, A J, and SCHULHOF, K Further attempts to increase experimentally the hormone output by thyroid gland, Am Jr Physiol, 1927, lxxxi, 661-664
- 23 SCHULHOF, K Effect of antithyroglobulin on physiological action of thyroglobulin, Am Jr Physiol, 1930, xciii, 175-177
- 24 LOFF, L Mechanisms in development of active resistance to effects of substances stimulating thyroid gland in guinea pig, Science, 1934, lxxx, 252-253
- 25 TWOMBLY, G H, and FERGUSON, R S Protective substances in sera of animals injected with anterior pituitary-like hormone of teratoma testis urine, Proc Soc Exper Biol and Med, 1934, xxxii, 69-71
- 26 MEYER, R K, and GUSTUS, E L Refractoriness to ovarian stimulation in rhesus monkey, Science, 1935, lxxxii, 208-210
- 27 EITEL, H, and LOESER, A Naunyn-Schmiedeberg's Arch, 1935, clxxvii, 737
- 28 SCOWEN, E F, and SPENCE, A W Effect of prolonged administration of acid extract of anterior pituitary on thyroid gland of guinea pig, British Med Jr, 1934, ii, 805-807
- 29 ROGOWITZ, N Die Veränderungen des Hypophyse nach Entfernung der Schilddrüse, Beitr z path Anat u z allg Path, 1888-1889, iv, 453-470
- 30 ADLER, L Metamorphosestudien an Batrachienlarven, Arch f Entwicklungsmech d Organ, 1914, xxxix, 21-45
- 31 ALLEN, B M Biol Bull Woods Hole, 1919, xxxvi, 405
- 32 SMITH, P E, and SMITH, I P Repair and activation of thyroid in hypophysectomized tadpole by paracental administration of fresh anterior lobe of bovine hypophysis, Jr Med Res, 1922, xiii, 267-283
- 33 SPAUL, E A Activity of anterior lobe pituitary, Jr Exper Biol, 1930, vii, 49-87
- 34 UHLFATHUTH, E, and SCHWARTZBACH, S Anat Rec, 1926, xxxiv, 119
- 35 SMITH, P E Disabilities caused by hypophysectomy and their repair, Jr Am Med Assoc, 1927, lxxxviii, 158-161
- 36 FOSTER, G L, and SMITH, P E Hypophysectomy and replacement therapy in relation to basal metabolism and specific dynamic action in rat, Jr Am Med Assoc, 1926, lxxxvii, 2151-2153

- 37 LOEB, L, and BASSETT, R B Comparison of effects of various preparations of anterior pituitary gland on thyroid of guinea pig, *Proc Soc Exper Biol and Med*, 1930, **xxvii**, 490-492
- 38 ARON, M Action de la prehypophyse sur la thyroïde chez le cobaye, *Compt rend Soc Biol*, 1929, **cii**, 682-684
- 39 a COLLIP, J B, and ANDERSON, E M Production of serum inhibitory to thyrotropic hormone, *Lancet*, 1934, 76-78
b ANDERSON, E M, and COLLIP, J B Preparation and properties of antithyrotropic substance, *Lancet*, 1934, 784-786
- 40 BLACK, P T Inactivation of insulin by normal and diabetic blood, *Brit Jr Exper Path*, 1933, **xiv**, 318-322
- 41 a COLLIP, J B Placental hormones, *Internat Clin*, 1932, **iv**, 51-70
b MCPHAIL, M K Effect on reproductive organs of rat of prolonged treatment with ovary-stimulating substances, *Jr Physiol*, 1933, **lxxx**, 105-112
- 42 a SELYE, H, COLLIP, J B, and THOMSON, D L Loss of sensitivity to anterior pituitary-like hormone of pregnancy urine, *Proc Soc Exper Biol and Med*, 1934, **xxxv**, 487-488
b SELYE, H, COLLIP, J B, and THOMSON, D L Loss of sensitivity to gonadotropic hormone of hypophysis, *Proc Soc Exper Biol and Med*, 1934, **xxxv**, 566
c SELYE, H, BACHMAN, C, THOMSON, D L, and COLLIP, J B Further studies on loss of sensitivity to anterior pituitary-like hormone of pregnancy urine, *Proc Soc Exper Biol and Med*, 1934, **xxxv**, 1113-1115
d BACHMAN, C, COLLIP, J B, and SELYE, H Anti-gonadotropic substances, *Proc Soc Exper Biol and Med*, 1934, **xxxv**, 544-547
- 43 BACHMAN, C *Proc Soc Exper Biol and Med*, 1935, **xxxvii**, 851
- 44 COHEN, S L, MARRIAN, G F, and WATSON, M *Lancet*, 1935, 674
- 45 a COLLIP, J B Placental hormones, *Can Med Assoc Jr*, 1930, **xxiii**, 631-633
b COLLIP, J B, BROWNE, J S L, and THOMSON, D L Relation of emmenin to other estrogenic hormones, *Jr Biol Chem*, 1932, **xcvii**, pages **xxvii-xxviii**
c BROWNE, J S L Chemical and physiological properties of crystalline estrogenic hormones, *Can Jr Res*, 1933, **viii**, 180-197
- 46 HOFFMANN, F, and ANSELMINO, K J Das Fettstoffwechselhormon des Hypophysenvorderlappens, *Klin Wehnschr*, 1931, **x**, 2383-2386
- 47 MAGISTRIS, H Das Fettstoffwechselhormon des Hypophysenvorderlappens, *Endokrinol*, 1932, **xi**, 176-191
- 48 BURN, J H, and LING, H W Excretion of acetone bodies on fat diet as affected by injection of pituitary (anterior lobe) extract and by pregnancy, *Quart Jr Pharm and Pharmacol*, 1933, **vi**, 31-38
- 49 BUTTS, J S, CUTLER, C, and DEUEL, H J Sexual variation in carbohydrate metabolism, role of anterior pituitary in metabolism of diacetic acid, *Jr Biol Chem*, 1934, **cv**, 45-58
- 50 BLACK, P T, COLLIP, J B, and THOMSON, D L Effect of anterior pituitary extracts on acetone body excretion in rat, *Jr Physiol*, 1934, **lxxxvii**, 385-391
- 51 BLACK, P T *Jr Physiol*, 1935, **lxxxviii**, 15
- 52 LONG, C N H, and LUKENS, F D W Effect of adrenalectomy and hypophysectomy upon experimental diabetes in cat, *Proc Soc Exper Biol and Med*, 1935, **xxxvii**, 743-745
- 53 ANDERSON, E M, and COLLIP, J B Studies on physiology of thyreotropic hormone of anterior pituitary, *Jr Physiol*, 1934, **lxxxviii**, 11-25
- 54 BATFS, R W LAHR, C L, and RIDGLE, O Gross action of prolactin and follicle-stimulating hormone on mature ovary and accessories of fowl, *Am Jr Physiol*, 1935, **cvi**, 361-368

EXPERIMENTAL AIR EMBOLISM *

By JOSLPH B WOLFFE, M D , and HAROLD F ROBERTSON, M D ,
Philadelphia, Pennsylvania

THE literature contains many case reports and a number of experimental studies of air embolism, but opinions still differ widely regarding its clinical significance and its mechanism

Hobart Hare, in 1902, injected 60 c c of air into the jugular vein of a dog without the production of any symptoms whatever In two patients, 2 to 3 c c of air were injected into the median basilic vein without ill effects W H Luckett, in 1913, reported a case of air embolism in the lateral ventricles of the brain following a fracture of the skull in which the air was probably forced into the ventricles, during an attack of sneezing, through a fracture in the frontal sinus Death occurred 21 days after this accident, and necropsy proved the presence of air in the ventricles

Edward von Adelung cites the instance of a man with pulmonary tuberculosis and pleural adhesions who, while undergoing an artificial pneumothorax, developed paralysis of the right arm and leg, cyanosis, cardiovascular shock, and unconsciousness He completely recovered the next day There have been a number of similar reports of air embolism following artificial pneumothorax

Charles Pierre Mathe reported a case of fatal embolus due to inflation of the bladder with air Here the formation of emboli took place, he claimed, by the entrance of air into the venous circulation, either through an ulceration of the mucosa caused by some preexisting pathological lesion such as ulcer, tumor, or laceration or as a result of injury to the mucosa from over-distention of the bladder Death occurred as soon as the patient became convulsed and cyanotic

Ewald and Kobert conclude after experimentation, that air may traverse the intact lung tissue and escape into the blood vessels or pleural cavity when intrapulmonary pressure is greatly increased

The occurrence of air embolism of the retinal vessels of man and rabbits was described by Hans Barkan in 1928 The retinal arteries became completely filled with air and the entire fundus contained innumerable fine glittering lines These hung together like spider webs and formed an extraordinarily fine network over the whole fundus This condition has been observed in man following puncture of the maxillary antrum, and as a result of intracranial or neck surgery

An interesting report of air embolism occurring during pneumarthrosis of the knee joint is given by Samuel Kleinberg He injected oxygen at low pressure into the knee joint The injection lasted only half a minute when suddenly the patient became pulseless The pupils dilated widely and un-

* Received for publication March 9, 1935

consciousness ensued. With improvement of circulation, resulting from the administration of stimulants, the patient became wildly delirious, requiring the strength of several attendants to hold him. Within a few days he completely regained consciousness and his further recovery was uneventful.

Allen and Clark conclude that simple thoracentesis may produce a bronchovenous fistula which will serve as a portal of entry for air into the pulmonary veins. They claim that experimental work on dogs demonstrated gravity as a determining factor in the distribution of air, when the head was elevated, the head, neck and forelegs received air, when the head was depressed, the trunk and hind legs received the air and the coronaries were heavily involved. The air tended to float on the blood and to seek the upper parts of the body. Even where the stream is rapid and violently churned, as in the heart and aorta, air and blood fail to mix thoroughly. Air may remain stationary in the bend of a vessel or, should gravity dictate, it may even pass in the direction opposite to that of the blood.

The literature reveals three schools of thought regarding the causation of death from air embolism. The first accepts a cerebral death, the second a respiratory death, with suffocation ensuing from obstruction of the pulmonary artery, and the third, a cardiac death. The last is thought to be caused by a lowering of intracardiac pressure and circulatory failure.

The purpose of our investigation is merely to show the course pursued by air, when injected into a peripheral vein, and its effects.

PROTOCOL

Experiment A A daily injection of 0.5 c.c. of air was administered to rabbits, weighing approximately 2.5 kilo, for five days without any untoward effects. This was gradually increased. When 2 c.c. (average) were administered at one time, the rabbits developed convulsions and died within three minutes. As long as less than 2 c.c. (average) was administered, and sufficient time allowed between injections, the rabbits recovered.

Experiment B Five c.c. of air were given to a dog weighing 15 kilo, as rapidly as one could inject it into the femoral vein, without any untoward results. The dose was doubled every day until 50 c.c. were reached and still there were no ill effects. As we increased the amount to 75 c.c. the animal became dyspneic, listless and the mucous membrane showed a cyanotic hue. But, in about five minutes, the dog made a complete recovery. The air dose was administered again daily for one week. Similar experiments were carried out on a few other animals. When the dose was doubled to 150 c.c. the animals became extremely ill, markedly cyanotic and dyspneic with a marked pulling of the intercostal muscles, but after 15 minutes they recovered. It was only after the amount was increased to 250 c.c. that the animal died. These experiments were repeated with similar results.

Experiment C In an average sized dog, we have cut the veins of the neck, laid them open and yet by pressing and relaxing the thorax (the

method used in artificial respiration) we have been unable to introduce air into the circulation. A small amount of air could be felt passing along the vein for about a quarter of an inch if a funnel attached to a cannula was raised about two feet above the neck of the animal. There were no untoward effects and upon removal of the cannula blood again appeared at the proximal end of the vein.

Experiment D An overdose of morphine and chlorotone was given to some animals after small amounts of air had been injected (1 c c to rabbits and 20 c c to dogs). The large vessels were ligated wherever possible and the organs then sectioned under water. The only place where air was consistently found was in the pulmonary artery and its branches. In those animals where the amount of air given was above the lethal dose, the air was found in the right ventricle, the coronary veins, right auricle and even in the superior and inferior vena cava if the amount injected were large enough. At no time, however, did we find air on the left side of the heart or in any other organ.

CONCLUSIONS

1 The amount of air necessary to produce death when injected intravenously differs with each animal (rabbits and dogs) and seems to be directly proportional to the size of the pulmonary artery and its branches. The lethal dose for a rabbit is approximately 0.5 c c per kilo, while in a dog it is 15 c c per kilo.

2 The injected air is found in the pulmonary artery and its branches. Only if the volume of air injected is in excess of the volume of the pulmonary artery and its branches, will it be found in the right ventricle, right auricle and in the superior and inferior vena cava. No air could be found in the left side of the heart or in any of the other organs after sectioning them under water. The air, when introduced intravenously, did not go against the blood stream in spite of variations in gravity.

3 The effect of the air is that of a circulatory tampon blocking the pulmonary circulation.

4 We were rather surprised that the speed of injection was of little importance. No matter how slowly it was injected, the air accumulated in the pulmonary artery and its branches. As long as the injection period was shorter than the absorption period, the result was about the same.

5 If a large volume of air is accidentally injected intravenously—judging from the signs seen in animals—the following may be looked for: shock, dyspnea, cyanosis, slow pulse, convulsions and death.

6 In cases where a large volume of air is accidentally injected it would be logical to aspirate the right ventricle since it is easily accessible.

7 The amount of air which may be accidentally introduced in humans during an ordinary intravenous injection should occasion no clinical manifestations.

BIBLIOGRAPHY

- MATHÉ, C P Fatal embolus due to inflation of bladder with air, *Surg, Gynec and Obst*, 1929, *xlvi*, 429-436
- VON ADELUNG, E A case of gas embolism, *Jr Am Med Assoc*, 1917, *lxix*, 1522
- LUCKETT, W H Air in the ventricles of the brain, following a fracture of the skull, *Jr Ment and Nerv Dis*, 1913, *xi*, 326-328
- HARE, H A The entrance of air into the veins, *Am Jr Med Sci*, 1902, *cxiv*, 843-847
- LAWHORN, C C The fallacy of air embolism as a cause of death in obstetrical and surgical cases, *Surg, Gynec and Obst*, 1915, *xx*, 498
- QUITTNER, S S Report of a case of air embolus by way of lateral sinus—reaction and untoward recovery, *Laryngoscope*, 1921, *xxx*, 603
- BLAIR, V P, and MCGUIGAN, H A suggestion for the treatment of air embolism, *Weekly Bull St Louis Med Soc*, 1910, *iv*, 267-269
- BLAIR, V P, and MCGUIGAN, H A suggestion for the treatment of air embolism, *Ann Surg*, 1910, *lii*, 471-486
- VAN ALLEN, C M, HDINA, L S, and CLARK, J Air embolism from pulmonary vein, *Arch Surg*, 1929, *xix*, 567-599
- NORDLAND, M, HALL, B E, and St Oyr, K I Air embolism in thyroidectomy, with experimental study, *West Jr Surg, Obst and Gynec*, 1931, *xxxix*, 581-591
- BAUM, F The x-ray diagnosis of pneumothorax accidents and air embolism, *Am Med*, 1933, *xxii*, 271-276
- KLEINBERG, S Pulmonary embolism following oxygen injection of knee, *Jr Am Med Assoc*, 1927, *lxxxix*, 172-173
- JOANNIDES, M, and TSOULOS, G D The etiology of interstitial and mediastinal emphysema, *Arch Surg*, 1930, *xc*, 333-339
- RUKSTINAT, G J, and LECOUNT, E R Air in coronary arteries, *Jr Am Med Assoc*, 1928, *xc*, 1776-1779
- JACKSON, C, and BABCOCK, W W Coronary air embolism, *Surg Clin N Am*, 1930, *x*, 1265-1269
- CASTERO, A Embolism and thrombosis of central retinal vessels, *Can Med Assoc Jr*, 1928, *xi*, 344-345
- BARHAM, H Air embolism, *Trans Am Ophthalmol Soc*, 1927, *xxv*, 224-236
- PARRY, T G W Bilateral embolism of central retinal artery, *Brit Med Jr*, 1928, *i*, 178
- BUTLER, T G Retinal embolism, *Trans Ophthalmol Soc of United Kingdom*, 1927, *xlvi*, 384
- BARKAN, H Air embolism in retinal vessels, *Arch Ophthalmol*, 1928, *lvii*, 402-411

RECENT ADVANCES IN CARBOHYDRATE METABOLISM WITH PARTICULAR REFERENCE TO DIABETES MELLITUS *

By C N H LONG, M D , D Sc , *Philadelphia, Pennsylvania*

SINCE the discovery of von Mering and Minkowski some 46 years ago, that total extirpation of the pancreas in animals produced a condition indistinguishable from diabetes mellitus in man, three major problems have confronted both physiologists and clinicians interested in this disease. They are 1 The isolation and clinical application of the internal secretion of the pancreas 2 The mode of action of this pancreatic hormone 3 The elucidation of the mechanisms involved in the production of the diabetic syndrome

The first problem was solved in 1922 when Banting and Best succeeded in preparing insulin. This discovery was at once followed by the world-wide use of this substance in clinical diabetes with the happy results that we are all familiar with today.

In spite of the enormous volume of work upon the subject the mechanism of insulin action is at present but ill defined. It would appear to be fairly well established that insulin has a dual action leading to increased tissue (chiefly muscle) utilization of glucose and to a decreased formation in the liver of glucose from non-carbohydrate sources.

The essential problem still remains unsolved. Briefly this is, what alterations are produced by insulin in the glucose molecule that enable it to be so easily metabolized? Several workers have attempted to show that in the presence of insulin glucose is converted into an active form readily utilizable by the cell. None of these attempts have been successful and at the present time we must admit our inability to explain this fundamental property of insulin.

It is in the elucidation of the third problem that considerable headway has been made in recent years. This problem is "What mechanisms are involved in the production of the diabetic syndrome which occurs following total pancreatectomy in animals or as a result of disease in man?" The sequence of events in either of the above cases is as follows (a) marked hyperglycemia and glycosuria which persist during fasting, (b) increased protein breakdown and conversion to glucose, as is indicated by the high nitrogen excretion and the constancy of the urinary glucose-nitrogen ratio, (c) the appearance of large amounts of aceto-acetic and beta-hydroxybutyric acid in the urine, (d) the quantitative excretion of ingested carbohydrate along with the failure of the respiratory quotient to rise above the level

* Read at the Philadelphia meeting of the American College of Physicians, May 3, 1935

From the George S. Cox Medical Research Institute, University of Pennsylvania, Philadelphia

indicating fat oxidation when such carbohydrate is given, (e) the development of severe acidosis, coma and finally death

Two theories have been advanced to explain the above series of events. The first of these may be termed "the failure to utilize glucose." The proponents of this idea hold that in the absence of insulin there exists an almost complete inability of the cells to oxidize glucose. This deprivation of carbohydrate in turn throws the burden of supporting the metabolism upon protein and fat. The increased utilization of protein accounts for the high urinary nitrogen and the constant glucose-nitrogen ratio in the urine, since a constant proportion of protein is assumed to be converted into glucose. The increased amounts of fatty acids that are mobilized are broken down in the usual manner as far as aceto-acetic and beta-hydroxybutyric acids. The further metabolism of these substances to CO_2 and water is, however, held to be dependent upon the oxidation of a certain proportion of glucose. From this assumption has arisen the aphorism that the fats burn in the flame of the carbohydrates. From a biochemical point of view this relationship has been spoken of as the ketogenic-antiketogenic ratio, or the fattyacid—glucose ratio. Since, as we have seen, a virtual absence of glucose oxidation is held by this school to be the essential defect, it is obvious that if the ketogenic-antiketogenic ratio is a biological rule, then these ketone bodies must accumulate to a marked degree in diabetes, since there is not only a failure to metabolize them but also an increased production of them as the fat stores of the body are drawn upon in increased amounts. As a result they accumulate in the blood and tissues and are a contributory factor in the development of the acidosis and coma.

In 1901 the discovery of Blum¹ that the injection of epinephrine was followed by hyperglycemia and glycosuria gave rise to the theory that this substance was the physiological antagonist of the internal secretion of the pancreas. The Vienna School headed by Von Noorden, Falta, and others built up an elaborate theory of glandular interrelationships between the thyroid, adrenal medulla and the pancreas to explain the effects of pancreatectomy. This view has come to be known as the "over-production theory." In brief, their main arguments were that the diabetic condition is not entirely brought about by a failure to metabolize glucose, but rather by an over-production of this substance from protein and fat. Furthermore, using the glycosuric action of epinephrine as their argument, they indicated that the uncompensated action of the adrenal medulla in the absence of the pancreas brought about this over-production. In brief, diabetes mellitus was in reality hyperadrenalism.

The collective work of many investigators has exposed the falseness of this view. In the first place, epinephrine although producing glycosuria and depletion of liver glycogen, does not stimulate protein metabolism nor will it produce the degree of ketonuria observed in diabetes. Nor does its continued injection produce a persistent glycosuria such as is seen even in the fasting diabetic animal. More recent work of the Coris² has demon-

strated that epinephrine, although at first reducing liver glycogen, finally brings about a marked increase in this substance at the expense of the muscle glycogen. It would appear at the present time that the effects of epinephrine are limited to the formed carbohydrate elements in the body and that it is incapable of stimulating gluconeogenesis from protein, which after all is the most characteristic metabolic disturbance in diabetes mellitus.

Until recent years the theory that the essential factor in the causation of the diabetic condition is a failure to oxidize glucose has been accepted by the majority of competent workers in this field. All the experimental evidence favored this view while the work advanced by the supporters of the pluri-glandular hypothesis has in general either been poorly conceived or else capable of satisfactory explanation in the terms of the opposing view.

The differences between these two schools are not confined to those concerning diabetes alone. As mentioned above, the over-production theory contends that the conversion of fatty acids to glucose is one of the factors creating the excessive sugar production in diabetes. It is a logical assumption that this transformation of foodstuffs is a normal phenomenon and that the absence of insulin allows this conversion to proceed in an unchecked and exaggerated manner. This is not yet generally accepted, and, in fact, there is no experimental evidence to support such a view. It is, however, agreed that there is excessive production of glucose from protein, but the first school looks upon this as a consequence of failure of glucose oxidation, while the second holds it is a primary feature of the diabetic state induced by the uncontrolled action of the contra-insulin hormones. The failure to ascribe to epinephrine this antagonistic rôle and the absence of evidence as to any other substance acting in this manner placed the over-production theory in a precarious position.

This sharp difference of opinion has to some extent been cleared up by the work of recent years. Thus it had long been noted in acromegaly, which is associated with tumors of the anterior pituitary, that glycosuria and diabetes were exceedingly frequent complications. Furthermore, since the discovery of insulin, the observation was made that hypophysectomized animals were exceedingly sensitive to this hormone, indicating that some normally antagonistic action to its injection was absent.

About 1927 Houssay and his associates³ began the publication of a long series of papers concerning the effect of previous hypophysectomy upon the diabetes following total extirpation of the pancreas. This work, for the light it has already thrown upon the diabetic state and the possibilities it has opened for future knowledge of this condition, entitles it to be ranked with that of Minkowski, and Banting and Best as a milestone in our knowledge of this disease.

Houssay's first experiments were carried out upon toads. They were, however, rapidly extended to dogs. The findings in both species were as follows: 1. After pancreatectomy in an hypophysectomized animal the degree of hyperglycemia and glycosuria was much diminished compared to

that following pancreatectomy in an intact animal 2 The nitrogen excretion and the dextrose-nitrogen ratio in the urine were also decreased 3 Ketonuria was markedly reduced and diabetic acidosis and coma did not occur 4 As a consequence of these changes the animals survived for a long period The diabetes was not entirely obliterated, but was transformed from a rapidly fatal condition into one of mild degree Thus dogs which ordinarily live only about two weeks after pancreatectomy survived for six months or more if the hypophysis was also removed 5 These doubly operated animals were extremely liable to hypoglycemic episodes especially if fasted, glucose injections being often necessary to save their lives 6 The carbohydrate tolerance, although not normal, was often greatly superior to that of the control depancreatized group 7 Marked loss of weight occurred in all the doubly operated animals that survived for long periods, and in fact these animals ultimately succumb to inanition This loss of weight is in part to be attributed to the absence of the external pancreatic secretion and partly to the mild diabetic state that persists

In the first experiments upon toads Houssay⁴ was able to show that implantation of the anterior lobe of the pituitary brought about a return of the diabetes to its usual severity Similar experiments in dogs were at first unsuccessful but in more recent work he⁵ has made use of alkaline extracts of bovine anterior pituitaries With these extracts Houssay was able to exaggerate markedly the diabetic state of his doubly operated dogs He⁶ has also reported that these extracts produce hyperglycemia and glycosuria in normal animals In this he is supported by Evans,⁷ Baumann and Marine⁸ and others

For my own part, up to the present I have not seen highly purified anterior pituitary extracts produce this effect in normal animals, and other workers have reported similar negative results⁹ The production of a persistent diabetes in normal animals by anterior pituitary injections is only one of the many problems that await future investigation

How are we to explain these findings in the light of the present theories of diabetes? It appears to me that Houssay has conclusively demonstrated the participation of the anterior pituitary hormones in the sequence of events following total pancreatectomy

Thus, in the absence of these hormones, sugar production from protein is decreased and to judge from the urinary dextrose-nitrogen ratio a greater portion of the glucose formed from protein is utilized Furthermore, the capacity of the tissues to utilize carbohydrate as judged from the carbohydrate tolerance is increased

Even more striking is the virtual absence of ketonuria This would imply that the mobilization of fat is decreased or else that the ketone bodies are being normally metabolized as might be expected if carbohydrate oxidation was resumed

It will at once be realized that here is the first satisfactory evidence in favor of the pluri-glandular or over-production hypothesis The anterior

pituitary hormones may well be the long sought contra-insulin hormones. Their action would be expected to drive up sugar production in the liver from protein, and possibly to decrease the capacity of the tissues to utilize glucose. Neither of these points is yet settled, but we do know that the injection of these anterior pituitary hormones confers upon the organism marked resistance to the usual effects of insulin. In seeking an explanation of the manner by which these effects are produced it should not be forgotten that hypophysectomy causes marked changes in other organs of the body. Thus there occurs atrophy of the gonads, thyroid and adrenals and probably of the parathyroids and thymus. Now it is already known that alterations, particularly excess of the thyroid secretion, cause disturbances in carbohydrate metabolism. Houssay³ and his co-workers have shown that thyroidectomy does not influence the course of a total experimental diabetes in dogs. We may therefore dismiss for the present the possibility that it is absence of the thyroid secretion that is responsible for these changes in the diabetes of hypophysectomized animals.

The only other gland whose secretions are known to influence carbohydrate metabolism is the adrenal. This is a double gland consisting of a cortical portion necessary for life and a medulla which is an integral part of the sympathetic nervous system. The medullary secretion is epinephrine and we have already narrated the failures to confer diabetogenic properties upon this substance. However, when we examine the adrenals of hypophysectomized animals the remarkable fact is found that the atrophy is limited to the inner layers of the cortex, the medulla remaining intact.

The establishment of the effects of hypophysectomy upon diabetes coupled with this atrophy of the adrenal cortex that follows hypophysectomy has stimulated fresh interest in the possible effect of the adrenals upon diabetes. In the past, many experimenters have attempted with indifferent success to prepare animals in which both the adrenals and pancreas had been removed. The short survival of such preparations has precluded any attempts to evaluate the results obtained. It has, however, been abundantly demonstrated that removal of the adrenal medulla alone or suppression of its secretion by section of its nerve supply does not prevent the characteristic sequence of events when the pancreas is subsequently removed.

In spite of this fact, Barnes and his co-workers¹⁰ have recently begun another investigation upon the effects of suppression of epinephrine secretion upon pancreatic diabetes in the dog. They have found that in certain dogs such a procedure produces some amelioration of the diabetes, this effect, however, is inconstant. Of greater interest is their finding¹¹ that the amounts of insulin required to maintain such animals is often only a fifth or a quarter of the amounts required when the adrenal medullae are active. If epinephrine is infused at a physiological rate into such animals the insulin requirement promptly returns to normal.

The work of de Takats and his associates¹² is closely related to that of Barnes. These workers have shown that section of the splanchnic nerves,

celiac ganglionectomy or denervation of the adrenals, results in a decreased insulin requirement both in dogs and in human diabetics. This work is still incomplete and at the present time there is no satisfactory explanation of the results obtained by these workers. In interpreting these experiments it should be remembered that epinephrine does not alter the nitrogen metabolism and there is good reason for believing that its effects are limited to the formed carbohydrate stores of the body. There is no doubt, however, that it acts as an antagonist to insulin so far as these stores are concerned since it is poured into the blood stream in response to an insulin hypoglycemia and causes a prompt discharge of liver glycogen and a consequent increase in blood sugar.

About 16 months ago my associates, Drs. Lukens and Evans, and myself became interested in the rôle of the adrenal cortex in endogenous carbohydrate metabolism. In addition to the marked effect of hypophysectomy upon this organ we were cognizant of the fact that Britton and his associates had advanced the view that the prepotent function of this gland was in the regulation of carbohydrate metabolism. Thus Britton,¹³ Zwemer¹⁴ and others have shown that the marked hypoglycemia and low liver glycogen stores of adrenalectomized cats are relieved by injections of cortical extracts that will maintain such animals in good health. It should also be recalled that a low blood sugar level is a common finding in Addison's disease.

In our work we have used cats and have found it possible to remove both adrenals and the pancreas. Such animals have lived in reasonably good health for considerable periods of time (as long as 28 days) and thus the results obtained are not invalidated by the objection that we were dealing with moribund animals. In all our experiments cortical preparations have been injected daily but no insulin was given, since it seemed to us that in studying the effects of these procedures the absence of this hormone is essential if we wished to draw any conclusions as to their effects upon a total diabetes.

The results are of some interest and I hope I may be pardoned for introducing our own work in a review of this kind. In the first place the effect of a total adrenalectomy upon pancreatic diabetes is strikingly similar to that of hypophysectomy. Thus, (1) The hyperglycemia and glycosuria are much reduced. (2) The nitrogen excretion and D/N ratio are decreased. (3) Ketonuria is very slight and acidosis does not develop. (4) The survival of the animals is much increased. The totally depancreatized cat dies in about four days, while the usual length of life of the doubly operated animal in the absence of infection is about 2 to 3 weeks. (5) Hypoglycemic episodes are common. (6) There is occasionally some improvement of carbohydrate tolerance but we have not observed, either in these or in the hypophysectomized-depancreatized cats, such striking improvements as have been reported by Houssay, Barnes and others in the dog. In another series of experiments we have shown that it is the adrenal cortex and not the medulla that is responsible for these changes, since animals from

which the adrenal medulla is removed rapidly die of typical diabetes after pancreatectomy

While our work was in progress Hartman and Brownell¹⁵ have reported similar findings in cats. One of these animals survived two months.

We next attempted to restore the full diabetic condition by injection of various hormones. It will be recalled that in the hypophysectomized-depancreatized dogs Houssay was able to accomplish this by the injection of crude alkaline extracts of anterior pituitary. In our work we have used the anterior pituitary preparation of Squibb.* This extract in doses of 5 to 10 c.c. causes a marked and often fatal recurrence of ketonuria and acidosis in the hypophysectomized-depancreatized cat. It also slightly increases the glycosuria, but in a degree not at all comparable to that of the ketonuria. Thus nine such cats were injected while in good health, of these, eight showed a marked ketonuria, four dying in coma within 48 hours.

To our surprise, similar or larger injections of this extract into adrenalectomized-depancreatized cats did not affect the ketonuria or glycosuria. Thus eight such animals were injected. Seven did not respond, the eighth animal was found at autopsy to possess an accessory cortical body.

In both groups of animals epinephrine in doses as large as 10 mg. a day, although increasing the glycosuria, did not alter the urinary nitrogen or ketone bodies.

The above experiments strongly suggest that the ketogenic activity of anterior pituitary extracts may be mediated through the adrenal cortex. In this respect it will be recalled that the gonad and thyroid stimulating principles of the anterior pituitary are inactive in castrated or thyroidectomized animals.

It would appear that the pituitary extract we were using does not possess very marked glycosuric activity. Evidence has also been advanced from other laboratories that the glycosuric function of such extracts may be due to a principle separate and distinct from that causing ketonuria. It is obvious that further investigation of this possibility will be of great interest.

I think it is probable that both hypophysectomy and removal of the adrenal cortical tissue are altering the response to pancreatectomy by interference with the same metabolic mechanism. At the present time it would appear that in the absence of either of these internal secretions the marked formation of sugar from protein and the accumulation of the intermediary products of fat metabolism which usually follow pancreatectomy are greatly decreased.

Now pancreatectomy is not the only method by which sugar formation from protein can be stimulated. Another method is deprivation of food. During a fast the blood sugar is maintained by this mechanism. It has been observed that neither hypophysectomized nor adrenalectomized animals will withstand fasting. Such animals under these conditions develop hypo-

* We are indebted to Dr. J. J. Durrett of E. R. Squibb & Sons for a generous supply of this extract.

glycemia which may prove fatal unless relieved by glucose. Another way of stimulating gluconeogenesis is by the injection of the glucoside phloridzin. This substance alters the renal permeability to glucose so that large amounts of sugar are lost in the urine. As a consequence sugar formation from protein is greatly increased and large amounts of ketone bodies appear in the urine.

Houssay¹⁰ has shown that in hypophysectomized dogs the injection of phloridzin is followed by an atypical response. These dogs do not form nearly as much sugar from protein and in addition do not develop such a severe ketonuria as do the controls. My associate, Dr. Gerald Evans, has carried out similar experiments upon adrenalectomized rats. He finds that these rats excrete only 40 per cent of the sugar and 18 per cent of the ketones found in the normal control group. Animals in which only adrenal cortical tissue is left behave as do normal rats. Furthermore, Dr. Evans has made the interesting observation that exposure of rats to low oxygen pressures results in a new formation of sugar from protein, as is shown by the greatly increased amounts of liver glycogen and the increased urinary nitrogen excretion found after such an experiment. If only adrenal cortical tissue is left intact the rats still form this new liver glycogen at the expense of protein, but totally adrenalectomized or hypophysectomized animals do not respond in this manner.

We have seen then that four procedures by which sugar formation from protein is increased—to wit, pancreatectomy, fasting, phloridzinization, and exposure to low oxygen tensions—are relatively ineffective in the absence of either the hypophysis or the adrenal cortex. We have suggested that the hypophysis controls this sugar formation from protein through the adrenal cortex. This is tantamount to saying that the adrenal cortex contains a diabetogenic substance or a contra-insulin hormone. The question may then be asked as to why the cortical extracts that we have injected into the animals did not exert a diabetogenic action. There are two possibilities: (a) that sufficient extract was not administered to cause a total diabetic response, or (b) that these extracts did not contain this, at present, hypothetical factor. If the latter is true the adrenal cortex must contain at least two hormones, one necessary for the maintenance of a proper water and salt metabolism and another concerned with sugar production from protein and possibly other aspects of metabolism.

Much of what I have said in the latter part of this address is not yet firmly established, but I have chosen to discuss it here to justify the title of my address. Surely we are justified in assuming that out of all this recent work upon carbohydrate metabolism there will emerge knowledge of great importance to all who are engaged in the treatment of diabetes mellitus in man. Even at the present time we are confronted with the fact that diabetes mellitus is not necessarily always a disease of the pancreas. We are now entitled to consider that in some cases the defect is to be attributed to the overactivity of other glands of internal secretion.

In a like manner we must now admit that in diabetes mellitus the overproduction of sugar is not necessarily a consequence of failure to oxidize glucose, but that it may be due to the uncontrolled activity of other endocrine glands. This hyperactivity may be the primary cause of the disease or may be the result of an endocrine imbalance induced by a deficient or absent insulin supply.

Finally, it should be emphasized that a normal carbohydrate metabolism is not possible if the insulin supply is deficient. Removal of the contra-insulin hormones ameliorates the destructive conversion of the tissue substances into glucose. It does not reinstate the normal carbohydrate metabolism.

BIBLIOGRAPHY

- 1 BLUM, F. Über Nebennierendiabetes, *Deutsch Arch f Klin Med*, 1901, lxxxi, 146
- 2 CORI, C F. Mammalian carbohydrate metabolism, *Physiol Rev*, 1931, xi, 143-275
- 3 HOUSSAY, B A, and BIASOTTI, A. Hypophysis, carbohydrate metabolism and diabetes, *Endocrinology*, 1931, xv, 511-523
- 4 HOUSSAY, B A, and BIASOTTI, A. Hypophysektomie und Pankreasdiabetes der Krote, *Arch f d ges Physiol*, 1931, ccxvii, 239-250
- 5 HOUSSAY, B A, BIASOTTI, A, and RIETTI, C T. Accion diabetogena del extracto antero-hipofisario, *Revista de la Soc argent de biol*, 1932, viii, 469-481
- 6 HOUSSAY, B A, BIASOTTI, A, DE BENEDETTO, E, and RIETTI, C T. Accion diabetogena de los extractos antero-hipofisarios, *Rev de la Soc argent de biol*, 1932, viii, 563-569
- 7 EVANS, H M, MEYER, K, SIMPSON, M E, and REICHERT, F L. Disturbance of carbohydrate metabolism in normal dogs injected with hypophyseal growth hormone, *Proc Soc Exper Biol and Med*, 1932, xxix, 857-858
- 8 BAUMANN, E J, and MARINE, D. Glycosuria in rabbits following injections of saline extract of anterior pituitary, *Proc Soc Exper Biol and Med*, 1932, xxix, 1220-1223
- 9 HRUBETZ, M C. Pituitary hormones and the blood sugar level, *Proc Soc Exper Biol and Med*, 1935, xxxii, 842
- 10 BARNES, B O, SCOTT, V B, FERRILL, H W, and ROGOFF, J M. Effects of partial adrenalectomy on experimental diabetes and on sensitivity to insulin, *Proc Soc Exper Biol and Med*, 1934, xxxi, 524-525
- 11 BARNES, B O, DIX, A S, and ROGOFF, J M. Effect of adrenalin on insulin sensitivity of partially adrenalectomized and of hypophysectomized dogs, *Proc Soc Exper Biol and Med*, 1934, xxxi, 1145-1146
- 12 DE TARATS, G, FENN, G K, and TRUMP, R A. Splanchnic nerve section in juvenile diabetic, *Ann Int Med*, 1934, vii, 1201-1217
- 13 BRITTON, S W, and SILVETTE, H. Apparent prepotent function of adrenal glands, *Am Jr Physiol*, 1932, c, 701-713
- 14 ZWEMER, R L, and SULLIVAN, R C. Blood chemistry of adrenal insufficiency in cats, *Endocrinology*, 1934, xviii, 97-106
- 15 HARTMAN, F A, and BROWNE, K A. Relation of adrenals to diabetes, *Proc Soc Exper Biol and Med*, 1934, xxxi, 834-835
- 16 BIASOTTI, A, and HOUSSAY, B A. Phlorrhizin diabetes in fasting or fed hypophysectomized dogs, *Jr Physiol*, 1932, lxxvii, 81-91

THE INCIDENCE OF THE CLINICAL TYPES OF SYPHILIS IN MALES, IN PREGNANT AND NON-PREGNANT FEMALES *

By WILLIAM C MENNINGER, M D, F A C P, *Topeka, Kansas,*
and JAROLD E KEMP, M D, *Chicago, Illinois*

IN a series of studies of neurosyphilis we¹ reported the incidence of neurosyphilis in males, nullipara and multipara † In order to make a comparison of the incidence of neurosyphilis with other types of syphilis in the same groups we have reviewed 800 cases of syphilis as they were admitted to a large venereal disease clinic or were under routine treatment Our findings are reported in this paper

In the selection of these cases, patients with early syphilis as well as those with late syphilis, with minor pupillary or reflex changes not diagnostic of neurosyphilis, who had not had an examination of their spinal fluid, were excluded As was pointed out in the previous paper, the incidence of neurosyphilis is probably higher in this, a venereal disease clinic, than in the average medical clinic where syphilis is frequently discovered incidentally

The following table indicates the frequency of the various types of syphilis in these three groups

TABLE I
Incidence of Various Types of Syphilis in 800 Patients

	Nullipara 219 cases	Multipara * 148 cases	Males 400 cases
Early Syphilis (Early Latent, Secondary Early, Secondary Recurrent, Sero-Positive Primary, Sero-Negative Primary)	67 (30.6%)	21 (13.5%)	103 (25.8%)
Latent Late (Syphilis of two or more years' standing with no manifestations but a positive blood Wassermann)	65 (29.7%)	71 (48.0%)	84 (21%)
Late Syphilis (Visceral, Skin, Eye, Bone Cardiovascular, Upper Respiratory Tract)	11 (5.0%)	15 (10%)	25 (6.2%)
Neurosyphilis	76 (34.7%)	41 (27.7%)	188 (47.0%)

* An additional 33 cases were reviewed in which one or more pregnancies had occurred prior to the syphilitic infection In this group, 42 per cent showed some form of early syphilis, 12 per cent with some form of late syphilis other than neurosyphilis, and 46 per cent with neurosyphilis The group is too small to warrant interpretive conclusions and is excluded from the above figures, but accounts for the total of 800 cases

* Received for publication JANUARY 18, 1935

† In the group of multipara are included only those women with a history of one or more pregnancies, of at least five months' duration, subsequent to their syphilitic infection

DISCUSSION

An analysis of this table reveals some important differences in the three groups of patients worthy of special comment

(1) In early syphilis the highest percentage of cases (30.6 per cent) occurs in the nullipara in contrast to a slightly lower percentage in males (25.8 per cent) and a very much lower percentage in multipara (13.5 per cent). Obviously the most important reason for the differences between the groups of multipara and nullipara is the fact that pregnancy often suppresses the manifestations of early syphilis. In addition, as we have shown in the previous paper, the nullipara come for examination at an earlier age. They are, as a class, generally unmarried and are more frequently exposed to infection than the multipara. Eleven per cent were detected as the result of yearly exclusion examinations for venereal disease. In contrast, multipara are most often married, come for examination at a later age, actually are less open to exposure, and usually less concerned over the possibility of infection.

The incidence of early syphilis in males was 25.8 per cent. The reasons for the difference between this figure and the group of multipara is apparent from the above discussion. It is slightly less than in nullipara, explained chiefly, we believe, because 13 per cent of the males gave a definite history of early syphilis which had been unrecognized or neglected.

(2) In latent syphilis, the highest percentage is found in the multipara, 48 per cent, in contrast to 29.7 per cent in nullipara and 21 per cent in males. The high percentage in multipara is again accounted for mainly by the influence of pregnancy which by its inhibitory influence upon the disease fosters the development of latency. As a result, syphilis is often discovered through accidental incidents, such as the birth of a congenital syphilitic child, repeated miscarriages, or syphilis in the husband. Furthermore it is assumed that pregnancy also gives some kind of immunity against central nervous system invasion by syphilis, with the result that the disease in multipara remains most frequently in a latent stage. Supporting this contention is the fact that neurosyphilis in multipara is less frequent (27.7 per cent) than in either nullipara (34.7 per cent) or males (47.0 per cent). The comparatively low percentage of latent syphilis in males (21 per cent) is accounted for by the high percentage of neurosyphilis in this group.

(3) The late manifestations of syphilis (other than neurosyphilis) appear twice as frequently (10.0 per cent) in multipara as in nullipara (5.0 per cent). Males fall in between these groups (with an incidence of 6.2 per cent). The number of cases in these three groups is so small that we do not feel interpretive conclusions are justified. The figures suggest the possibility that pregnancy does not so adequately protect against late syphilis as neurosyphilis and when the assumed protective mechanism of pregnancy fails the disease is more severe than when this protection is entirely absent (as in nullipara).

SUMMARY

The analysis of 800 cases of all types of syphilis shows that in the nullipara group 30.6 per cent have early syphilis, 29.7 per cent latent late syphilis, 5.0 per cent late syphilis other than neurosyphilis, and 34.7 per cent neurosyphilis, the multipara group shows 13.5 per cent early syphilis, 48.0 per cent latent late syphilis, 15.0 per cent late syphilis other than neurosyphilis and 27.7 per cent neurosyphilis, the males show 25.8 per cent early syphilis, 21.0 per cent latent late syphilis, 6.2 per cent late syphilis other than neurosyphilis and 47.0 per cent neurosyphilis.

Noteworthy is the high percentage of early syphilis in nullipara, the high percentages of latent syphilis and late syphilis other than neurosyphilis in multipara and the high percentage of neurosyphilis in males. The determining factors in the difference between these groups are probably the influence exerted by pregnancy, the age of examination and the social and marital status of the patients.

REFERENCE

- 1 KEMP, J. E., and MENNINGER, W. C. The incidence of neurosyphilis in males, in pregnant and in non-pregnant females (In press)

A CLINICAL STUDY OF THE MILD GRADES OF HYPOTHYROIDISM *

By BLANTON P SEWARD, B A , M D , F A C P , *Roanoke, Virginia*

THE descriptions of the features of two children in whom no thyroid glands were found at autopsy by Curling ¹ in 1850, and of sporadic cretinism in England by Fagge ² in 1871, stimulated the interest of physicians in a disease hitherto not investigated. Fagge regarded "wasting of the thyroid body" as the probable cause of cretinism and he predicted with remarkable accuracy some of the symptoms that might result from a deficiency in the secretion of the thyroid in adults. Two years later Sir William Gull ³ reported two cases of the cretinoid state developing in adults. In discussing these cases he expressed the hope that "once the attention of the profession is called to these cases, our clinical knowledge of them will in proportion improve." Ord ⁴ in 1878, being much impressed with the mucin deposits in the subcutaneous tissues of adults, named the disease myxedema. The observations of the Reverdins ⁵ and of Kocher ⁶ in Switzerland, and of Semon ⁷ in England, pointed to an insufficient secretion of the thyroid gland as the cause of myxedema. Finally, the investigations of the committee appointed in 1883 by the Clinical Society of London showed that the disease is caused by changes of a destructive nature in the thyroid gland.

Immediately after the discovery of the cause, it became obvious that the successful treatment depended upon supplying thyroid substance from an external source. Victor Horsley, ⁸ in 1890, suggested the implantation of thyroid tissue. Following this suggestion Murray ⁹ conceived the idea of making an extract of sheep's thyroids for subcutaneous injection, and in 1891 he began treating a patient with myxedema with injections. E. L. Fox ¹⁰ and H. W. G. MacKenzie, ¹¹ independently of each other, in 1892 began the oral administration of thyroid preparations.

This briefly is the history of the discovery of the cause and of the treatment of myxedema. Of the milder grades of hypothyroidism nothing was known until recent years. With increasing knowledge of the function of the thyroid gland, and with instruments for estimating the basal metabolic rate, we are able to diagnose hypothyroidism earlier and to institute the proper treatment before myxedema develops.

During the past decade a number of articles on the mild grades of hypothyroidism have appeared in the literature. Higgins, ¹² in 1925, emphasized dryness of the skin, thin hair, indefinite pains, constipation, localized edema, and headache as symptoms of incipient hypothyroidism in individuals with a moderately decreased metabolic rate. He also stated that some of the patients in his series were nervous and had a rapid pulse rate. McLester, ¹³

* Received for publication May 1 1935

From the Medical Department of the Lewis-Gale Hospital

four years later, mentioned thyroid deficiency as a cause of poor health in a small group of individuals in whom a decreased metabolic rate was the only significant finding. Warfield¹⁴ has called attention to the bizarre nature of the symptoms associated with persistent, even though moderately, decreased metabolic rates. Charles H. Mayo¹⁵ has observed complications, mostly in the circulatory system, developing during the convalescence following surgical operations of any kind upon persons who are sensitive to cold weather, who tend to run a subnormal temperature, and who have a basal metabolic rate ranging between minus 12 and minus 20.

Other clinicians have directed attention to certain obscure symptoms associated with a decreased metabolic rate. Breckinridge¹⁶ stated in 1932 that a mild degree of hypothyroidism is a frequent cause of menorrhagia and metrorrhagia, and that it should be excluded before resorting to the curette, the roentgen-ray, radium or abdominal section in the treatment of these conditions. Thyroid deficiency, however, was known before the days of clinical metabolimetry to be a cause of uterine hemorrhage, for Salzman¹⁷ reported cases that were controlled by the administration of thyroid extract. Hinton¹⁸ mentioned hypothyroidism as a cause of abdominal pains in a small group of patients in whom the roentgen-ray examination and other laboratory procedures showed no evidences of pathological changes in the gastrointestinal tract, the gall-bladder or the urinary system.

Brown¹⁹ regarded mild hypothyroidism as a factor in the causation of chronic constipation of middle life, particularly in women of the obese type who have a lowered metabolic rate. Brown²⁰ also found a diminished secretion of hydrochloric acid in patients with metabolic rates of minus 20 or lower. Several years ago Lee²¹ spoke of the occurrence of vasomotor rhinitis in young adults that could be accounted for only on the basis of a low metabolic rate, and that was completely relieved by the administration of thyroid extract. Lawrence²² called attention to the loss of weight in contrast with the gain in weight in many patients with hypothyroidism. Hypercholesterinemia and also a partial or complete cessation of creatinine excretion have been found by several investigators^{23, 24, 25, 26} in all grades of hypothyroidism in adults and in children. These investigators have suggested that the level of the blood cholesterol might serve as a useful check on the severity of hypothyroidism since the basal rate does not always give a true picture, and the clinical impression is difficult to define. They suggested also that the level of the cholesterol may be a useful guide to the efficacy of thyroid therapy.

In a study of 53 patients with basal metabolic rates ranging between minus 12 and minus 38, and in whom a diagnosis of mild or moderate hypothyroidism was made, we have been impressed first, with the vague, indefinite character of the symptoms in contrast with the definite nature of the symptoms of myxedema; second, with the similarity of the symptoms with those either of organic disease or of functional disturbances in the different organs and systems of the body, and third, with the relatively frequent oc-

currence of hypothyroidism here in a section of the country where goiter is commonly seen

This group does not include patients who in the course of a general examination were found to have a low metabolic rate that improved without thyroid medication. Neither does it include several patients who had symptoms and signs of other endocrine disturbances associated with a low metabolic rate. Nor does it include one patient, a girl 22 years of age, who, at the time of the first examination had what appeared to be a colloid goiter with symptoms suggestive of hyperthyroidism even though the metabolic rate was minus 15. For one and a half years her rate remained constantly below minus 15, then her symptoms became more pronounced and the metabolic rate arose above the normal. Soon afterwards an adenomatous goiter was removed. The following table shows the age incidence

TABLE I
Age Incidence

Years	No. Cases
10 to 19	4
20 to 29	11
30 to 39	17
40 to 49	15
50 to 59	4
60 to 69	2

It is apparent that the greater number of patients in this series were between 30 and 49 years of age, and that almost an equal number were in the third and fourth decades of life. Females outnumbered the males, 4 to 1.

The appearance of symptoms in the majority of patients during middle life and in the years immediately preceding this period at once raises the question, what is the cause of hypothyroidism? The factors concerned in the etiology have not been satisfactorily determined. Plummer suggested atrophy of the thyroid gland, as a result perhaps of thyroiditis. Hertoghe²⁷ reported a great frequency of hypertrophied tonsils and adenoids in his cases of thyroid insufficiency. It is doubtful whether infections in the nasopharynx play a part in the causation of hypothyroidism, but since they are frequently found in children and young adults, it is possible that they may, in some instances, affect the thyroid gland causing inflammation and destructive changes, followed by atrophy. It is conceivable that during the earlier stages of atrophy the gland may still be able to secrete sufficient thyroxin to maintain the normal amount in the body tissues for some years, but as the stress and strain of life increase the supply diminishes, and the individual sooner or later becomes conscious of a sense of ill-being. Furthermore, it is possible that an illness producing toxemia, as toxemia of pregnancy, or puerperal infection, or influenza, may damage the gland to such an extent that it does not fully recover. We were unable, however, to obtain from our patients a history of an infection which we thought might have played a part in causing hypothyroidism. We are inclined to believe a constitutional

factor is operative in many of these patients whether or not they have a focus of infection. That there is a constitutional factor seems to be borne out by the fact that some people with hypothyroidism do not have symptoms.

Symptoms No definite symptoms or signs characterize the mild grades of hypothyroidism. In some cases the history seems an almost interminable story of disconnected symptoms, in other cases the symptoms are few and they may or may not be suggestive of hypothyroidism. The one symptom mentioned by nearly all of these patients, either voluntarily or upon close questioning, is ease of fatigue following mental or physical exertion. Many of these people hold responsible positions, although they are energetic, their work becomes burdensome and they are conscious of having to drive themselves to their tasks. A long rest makes them feel better, but after resuming their work the same weariness comes over them each day. Many of our patients with metabolic rates between minus 12 and minus 20 complained of being more easily fatigued than those with still lower rates.

In addition to fatigue, the chief complaint of one half the patients comprised varying degrees of mental depression, nervousness and irritability. These patients worried over the possible loss of their positions because they felt unable to render efficient service. Insomnia was complained of more frequently than drowsiness, even by those with the lowest basal rates.

Palpitation on exertion was conspicuous among the symptoms related by 20 patients, it was the chief complaint of three. The history of rapid heart action, fatigue and nervousness often suggested neuro-circulatory asthenia. One patient, a business man, 33 years of age, complained only of having had attacks of precordial pain for one month. The pain occurred more often late in the day or during the night, radiated into the left shoulder and arm, was accompanied by a sensation of a "heavy weight on the chest," and on two occasions it was only partially relieved by morphine.

Vague gastrointestinal disturbances, such as loss of appetite, fullness after meals, gas formation, abdominal distention, and occasionally nausea, are noted frequently in the histories. Two patients also complained of dull aching pains alternating with cramp-like pains in the lower abdomen, and another had had a dull pain in the left hypochondrium for six weeks. Constipation was also a common complaint, though it is doubtful whether it occurred much more frequently among the patients in this group than in a similar number suffering with other conditions.

Fourteen patients under 40 years and one past 60 years of age felt much concerned over a gradual loss of eight to twelve pounds in weight. Twelve patients above the age of 40 complained of a gradual increase in weight during the two preceding years even though they restricted their diets. The youngest patient in the group, a girl 12 years old, was brought by her mother for examination to determine the cause of an excessive gain in weight.

Eighteen patients mentioned headache, beginning usually in the vertex and radiating into the suboccipital region, as a prominent symptom. In two cases the headache was distinctly migrainous in character. In addition to

general weakness, four patients under 30 years of age complained of vague pains either in the joints or in the muscles. These pains simulated those due to foci of infections. Twelve patients admitted then were susceptible to colds, eight stated that they suffered with cold hands and feet. One complained only of a dry, itching skin. Three gave a history of irregular menstrual periods, in one the periods came on every two to three weeks and sometimes were profuse, while in two the periods often were delayed three or four weeks.

The average duration of symptoms in all cases was two and one-half years. Not infrequently the patient gave the impression of being neurotic, and in a few a neurotic element was present though it faded out of the clinical picture as the condition of the patient improved.

Physical Findings Hypothyroidism is found in both the sthenic and asthenic individual, though a larger number of our patients were of the asthenic type. Few had the calm, complacent or indifferent attitude usually observed in patients with myxedema. The majority of the patients appeared to be tired, yet they brightened up and for a time showed an interest in conversation.

Sixteen patients under 35 years of age were found to be definitely underweight, while two, including the girl 12 years old, were overweight. Twelve patients past 40 years of age were overweight, and two underweight. This finding would seem to indicate a tendency towards underweight in patients in whom a moderate degree of hypothyroidism manifests itself in the first half of life, and obesity in the second half. While difficult to explain, it seems logical to assume that during the developmental period of life, when the relative nutritive requirements of the body are at their maximum, any impairment of the oxidative processes of the body might result in a loss of weight. In other words, during this period of life the processes of anabolism are in excess of those of catabolism, and any reduction in the former might upset this balance, and result, therefore, in a retrograde effect.²⁸ This, of course, is purely a supposition. There seemed to be no relationship between the weight and the degree of thyroid insufficiency in our patients.

Equally interesting was the condition of the skin. Thickening of the integument was observed in seven patients above the age of 35, and in two between 20 and 25 years of age. Each of these patients, with one exception, had a basal rate ranging between minus 15 and minus 22. The exception was a patient with a rate of minus 32. The thick, smooth, papery feeling of the skin was the only manifestation of myxedema found in the entire group of patients. The changes in the integument, like the body weight, seemed to bear no definite relationship to the metabolic rate. It is interesting to note that the skin of another patient became thick, smooth and tight during the interval of two years when she failed to take thyroid extract. On the original examination in 1929 when the metabolic rate was minus 20, the skin felt normal. Two grains of thyroid extract daily maintained a normal

rate for three years. Then as she was feeling well she discontinued taking the drug. When she returned for examination two years later on account of a recurrence of symptoms, her skin had undergone the changes seen in a severe grade of hypothyroidism, although the basal rate was minus 20, as it had been five years previously. Thyroid extract again increased the metabolic rate, brought about relief from symptoms, and much improvement in the condition of the skin.

Moderate dryness of the skin, sometimes with desquamation on exposed surfaces, was found in 20 patients, a few fine wrinkles on the foreheads of several in the third and fourth decades of life, coarse wrinkles in one 25 years old, and in four past 40 years. Thinning and falling of the hair was found in several middle aged or past, but not to any greater extent, as far as we could tell, than is commonly seen at that time of life.

The rate of the heart varied in this as in any group of patients. Rates below 60 per minute were not found, although on the other hand, a moderate acceleration on several consecutive examinations after the patients had rested, was noted in 10 cases, including three with the lowest basal rates. The quality of the sounds varied as in other patients of the same age. The most striking change in the quality of the sounds was found in the young man who complained of attacks of precordial pain. His sounds were distant, the valvular element of the first sound predominated, the rate was 104, and the blood pressure 94 systolic and 60 diastolic. These findings and the history of precordial pain led us to suspect heart disease, even though the patient was young and gave no history of having had an infection that predisposes to cardiac disease. Two weeks of rest in bed and the administration of digitalis to the point of tolerance, however, did not bring about any improvement in the quality of the sounds, or any reduction in the rate. Then we thought of the possibility of hypothyroidism, but going further into the history we failed to elicit any suggestive symptoms. His metabolic rate nevertheless was found to be minus 28. Following the administration of thyroid extract the heart rate became normal, the quality of the sounds became normal, the blood pressure arose nearly to the normal level, and the pains ceased.

Eighteen of the 53 patients had a systolic blood pressure of 110 millimeters of mercury or less, with a proportionate reduction in the diastolic. While low blood pressure may often be associated with hypothyroidism, yet we do not think it was the cause of the hypotension in five patients as there was no significant elevation of the pressure following improvement in their metabolic rates and in their general condition.

The highest pressure, 190 systolic and 106 diastolic, was found in a woman 40 years of age, with a metabolic rate of minus 22. During the four years that she has taken thyroid extract the level of the blood pressure has continued practically unchanged. Another patient, 60 years of age, gave a history of having had hypertension for several years prior to our examination in 1929. At that time the pressure was 180 systolic and 100

diastolic, and the metabolic rate minus 24. She too has had to take thyroid extract most of the time. Her blood pressure has gradually come down to within normal limits, though she is subject to paroxysmal elevations which cause dizziness, headaches and unsteadiness of gait for three or four days. We do not think that there is any relationship in her case between the hypothyroidism and the hypertension.

Five patients between 25 and 40 years of age, and one 60 years old had visceroptosis, the greater curvature of the stomach lying well below the interiliac line, and the colon lying low in the pelvis. Since it is well known that ptosis of the stomach and colon may cause digestive disturbances, and lack of endurance, and since it is also known that people with visceroptosis sometimes have hypotension and low metabolic rates, the question as to what part the ptosis played in causing the symptoms arose in each case. Here we obtained help from the therapeutic test. Those patients with persistently low metabolic rates did not improve satisfactorily until they had taken thyroid extract, whereas other patients with ptosis and low basal rates not due to thyroid insufficiency improved readily without taking the drug.

Vasomotor rhinitis was found in four patients in early adult life by rhinologists who referred them for a general examination, including tests with allergens. The only significant finding was a low metabolic rate, ranging from minus 14 to minus 20. Thyroid extract brought about complete relief.

Infected tonsils were found in 19 patients, ethmoiditis in four, pyorrhea in four, cholecystitis in seven, and cervicitis in three. When analyzing all findings in each case, the question arose as to what part the focus of infection played in the causation of the symptoms and of the low metabolic rate? We at first regarded the low rate as being due to general weakness, secondary to the absorption of toxin over a long period of time and aggravated by the patient's mode of living. No satisfactory improvement was observed, however, in the majority of cases, following the usual methods of treatment and the clearing up of the foci of infection. Soon after the administration of thyroid extract each patient began improving and continued to improve until all symptoms subsided and the metabolic rate was normal. There seemed to be no significant difference in the subsequent course of the patients from whom the foci were removed as compared either with the patients from whom the foci were not removed, or with those who had no demonstrable foci.

Laboratory Findings. A moderate reduction in the erythrocytes or in the hemoglobin content or in both was found in one-third of the cases. A larger number of patients appeared to be anemic. Blood sugar estimations in 11 cases showed a normal sugar content. While this number is small, yet the figures do not indicate a hypoglycemic tendency such as Lawrence and Rowe²⁹ found in their patients with mild or moderate degrees of hypothyroidism. Estimation of the blood calcium of five patients, including those who had vasomotor rhinitis, showed a normal calcium content. One

of these patients five years later had a calcium content of 81 mg per 100 c c blood. Blood urea estimations in eight patients showed normal figures. We did not estimate the cholesterol content of the blood or the amount of creatine excreted in the urine of any patient.

Analysis of the stomach contents of 20 patients with gastrointestinal complaints showed a normal amount of hydrochloric acid in four, hypochlorhydria in 12 and hyperchlorhydria in one. The roentgen-ray examination showed visceroptosis in five cases and hypoperistalsis in one. Re-examination of the gastrointestinal tract of the latter patient 10 weeks later showed normal peristalsis. Presumably the improvement in the rate of peristalsis was due to thyroid extract which is known to increase the tone of the muscles of the intestine. Cholecystograms of seven patients with symptoms and signs suggestive of cholecystitis showed mild disturbances in the function of the gall-bladder.

The roentgen-ray examination of all patients who complained especially of palpitation, and also of the patient who complained of precordial pain, revealed no abnormality in the size or the shape of the heart, and no evidence of disease in the lungs. The electrocardiograms of these patients also were normal.

The urinalyses were normal except for a trace of albumin in several cases.

The one constant finding was a low metabolic rate ranging, as stated above, between minus 12 and minus 38.

Diagnosis We are aware of the criticism that may be directed against a diagnosis of hypothyroidism when the basal rate is as near the normal as minus 15. A diagnosis in these cases as well as in many with still lower rates can be made only after a prolonged period of observation. A rate of minus 12 or 15, and sometimes one falling within the lower limits of the normal range, may be significant, especially if associated with clinical evidences of a decreased energy production. Although it is unwise to make a diagnosis on the basal rate alone when it is only moderately decreased, still we believe a diagnosis is justified when the rate is persistently low, when it is associated with symptoms among which ease of fatigue is prominent, and when an improvement in both the rate and the symptoms is observed following the administration of thyroid extract. It does not seem necessary to make numerous laboratory examinations, in fact the average patient in private practice will not submit to numerous tests. It is not possible always to correlate the metabolic rate with the symptoms, for many patients with a moderately decreased rate have more pronounced symptoms than those with lower rates.

Hypothyroidism must be differentiated from hypopituitarism, hypovarianism, hyposuprarenalism, and starvation which all sometimes cause low metabolic rates. It must also be differentiated in some cases from neurocirculatory asthenia,¹ but more frequently from neurasthenia and tuberculosis. In a few of our cases the symptoms were so strongly suggestive

of hyperthyroidism that we were rather surprised to find the basal rate decreased instead of increased

Treatment The dose of thyroid extract or of the desiccated gland necessarily will vary according to the basal metabolic rate and the intensity of the symptoms. We usually prescribe from two to six grains daily, occasionally larger doses, rechecking the metabolic rate in about two weeks, and thereafter at such intervals as indicated. The subsequent dose of the drug will depend upon the improvement in the symptoms and in the metabolic rate. The response to treatment varied greatly in our patients. In some a prompt improvement was observed in both the symptoms and the rate, while in other cases the improvement was slow. Sometimes the symptoms subsided before the basal rate returned to the normal, and sometimes they persisted in a milder form after a normal rate was obtained. As a rule, the maximum improvement was not observed in our patients until their rates had been normal or nearly normal for several weeks. About one-half of these cases have not had to take the drug continuously, they have done well when leaving it off for intervals of a few weeks or occasionally for a few months, although if they go for longer intervals without taking it their symptoms recur. A few of these patients have learned from experience when to resume taking the drug. It is usually necessary also to prescribe mild sedatives, a mild laxative, dilute hydrochloric acid, and mild analgesics. Obviously these drugs are prescribed for the relief of the particular symptoms of which the patient complains and they may be discontinued in a few weeks. They may be needed again in the event of a recurrence of the symptoms.

Patients with hypothyroidism should be advised to rest regularly during the day and to retire early at night. The amount of rest naturally will depend upon the kind of work the patient is doing, the severity of the symptoms, and the metabolic rate. In some cases a complete rest for a few weeks is advisable, in the majority, however, this is not necessary.

In addition to prescribing drugs and regulating the habits, optimism is essential in the care of these patients. While thyroid substance will increase their strength, yet encouragement given by the physician carries them more easily through weary hours, gives them a brighter outlook and makes them happier. Life becomes more enjoyable as their ability to render more efficient service increases. And, what gives the physician greater satisfaction than helping his patient regain health and carry on his work more easily? The expression of gratitude of many of these patients calls to mind the words of John R. Oliver,²⁰ who said "To a physician, however, there is no pleasanter association or memory than the commingling of a past dependency and a present friendship."

CONCLUSIONS

1 Mild to severe grades of hypothyroidism are seen relatively frequently

2 There are no pathognomonic symptoms or signs. The most frequent and the most important single symptom is ease of fatigue. Other symptoms frequently mentioned are nervousness, palpitation, digestive disturbances, constipation, and various aches and pains. A loss of weight is often found in patients in whom thyroid insufficiency manifests itself in the first half of life and an increase in weight in those affected in later years. Mild grades of hypothyroidism may also be the cause of a few pronounced symptoms as vasomotor rhinitis and pains simulating those of heart disease. A thorough and comprehensive examination must be made in all cases.

3 A diagnosis is justified only when the symptoms are associated with a decreased metabolic rate. Often, however, the patient must be observed over a period of time before a diagnosis can be made.

4 The mild grades of hypothyroidism must be differentiated from other endocrine disturbances, such as hypopituitarism, hypoovarianism and hypoadrenalism, from chronic diseases such as tuberculosis, and from functional disturbances such as the neuroses and neurocirculatory asthenia.

5 The treatment consists of more than the administration of thyroid substance. Drugs for symptomatic relief should also be prescribed until the particular symptoms of which the patients complain subside. Rest and optimism are also important in the treatment. The maintenance dose of thyroid substance will depend upon the patient's sense of well being and the basal metabolic rate. The sense of well being will depend upon maintaining an adequate supply of thyroxin in the body tissues.

BIBLIOGRAPHY

- 1 CURRING, T. B. Two cases of absence of the thyroid body, and symmetrical swellings of fat tissue at the sides of the neck, connected with defective cerebral development, *Med-Chir Trans, Lond*, 1850, *xxviii*, 303.
- 2 FAGGE, C. H. On sporadic cretinism occurring in England, *Med-Chir Trans, Lond*, 1871, *liv*, 150. *Abstr. Proc Roy Med and Chir Soc, Lond*, 1871, *vi*, 329.
- 3 GULL, Sir W. W. On a cretinoid state supervening in adult life in women, *Trans Clin Soc Lond*, 1873, *vii*, 180.
- 4 ORD, W. M. On myxedema, a term proposed to be applied to an essential condition in the "cretinoid" affection occasionally observed in middle-aged women, *Med-Chir Trans*, 1878, *lxi*, 57.
- 5 REVERDIN, J. L., and REVERDIN, A. Note sur vingt-deux operations de goitre, *Rev med de la Suisse Rom*, Geneva, 1883, *iii*, 169, 233, 309.
- 6 KOCHER, T. Über Kropfexstirpation und ihre Folgen, *Arch f klin Chir*, 1883, *xxix*, 254-337.
- 7 SIMON, F. Discussion of myxedema, *Brit Med Jr* 1883, *ii*, 1079.
- 8 HORSLEY, V. Note on a possible means of arresting the progress of myxedema. *Brit Med Jr*, 1890, *i*, 287.
- 9 MURRAY, G. R. Note on the treatment of myxedema by hypodermic injections of an extract of thyroid gland of a sheep, *Brit Med Jr*, 1891, *ii*, 796.

- 10 FOX, E L A case of myxedema treated by taking extract of thyroid by mouth, Brit Med Jr, 1892, ii, 941
- 11 MACKENZIE, H W G A case of myxedema treated with great benefit by feeding with fresh thyroid glands, Brit Med Jr, 1892, ii, 940
- 12 HIGGINS, W H Incipient hypothyroidism clinical study, Jr Am Med Assoc, 1925, lxxxv, 1015-1017
- 13 MCLESTER, J S Thyroid deficiency as a cause of poor health, Med Clin N Am, 1929, vii, 1357-1367
- 14 WARFIELD, L M Hypothyroidism, Jr Am Med Assoc, 1930, xcvi, 1076-1080
- 15 MAYO, C H Thyroid deficiency, a commonly unrecognized disorder, West Jr Surg, 1933, vii, 427-430
- 16 BRICKNIDGE, S D Some practical aspects of hypothyroidism, Am Jr Obst and Gynec, 1932, lxxiii, 871-875
- 17 SALZMAN, S Hypothyroidism a factor in certain types of uterine hemorrhage, Am Jr Obst, 1916, lxxiv, 812-818
- 18 HINTON, J W Abdominal pain due to hypothyroidism, Jr Am Med Assoc, 1932, xcvi, 1702-1703
- 19 BROWN, T R Hypothyroidism as a cause of intractable constipation, Trans Assoc Am Phys, 1926, xli, 162
- 20 BROWN, T R The effect of hypothyroidism on gastric and intestinal function, Jr Am Med Assoc, 1931, xciii, 511-513
- 21 LEF, R I Vasomotor rhinitis and hypothyroidism, Med Clin N Am, 1925, viii, 1705-1708
- 22 LAWRENCE, C H Studies in endocrinology, hypothyroidism with and without myxedema, Boston Med and Surg Jr, 1924, cxc, 307-312
- 23 MASON, R L, HUNT, H M, and HURVITZ, L Blood cholesterol values in hyperthyroidism and hypothyroidism, New Eng Jr Med, 1930, cciii, 1273
- 24 BRONSTEIN, I P Studies in cretinism and hypothyroidism in childhood, Jr Am Med Assoc, 1933, c, 1661-1663
- 25 HESS, J H Blood cholesterol and creatine excretion in the urine as aids to diagnosis and treatment of hypothyroidism, ANN INT MED, 1934, viii, 607-611
- 26 PONCHER, H G, VISSCHER, M B, and WOODWARD, H Creatine metabolism in children with hypothyroidism, Jr Am Med Assoc, 1934, cii, 1132-1135
- 27 HERTOGHE, E Thyroid insufficiency Practitioner, 1915, xciv, 26-69, Med Rec, 1914, lxxvi, 489-505
- 28 BOND, W R, Professor of Physiology, Medical College of Va (Personal communication)
- 29 LAWRENCE, C H, and ROWE, A W Studies of endocrine glands, thyroid, endocrinology, 1928, vii, 377-450
- 30 OLIVER, J R A case in occupational therapy, Atlantic Monthly, 1935, clv, 160

PERNICIOUS ANEMIA WITH NORMAL BLOOD PICTURE ¹

By CONLEY H. SANFORD, M D , F A C P , *Memphis, Tennessee*

It appears established, from the experiments of Castle and his co-workers,^{1, 2, 3} that pernicious anemia is a deficiency disease due to the absence of an intrinsic factor of undetermined nature in the gastric secretion. This intrinsic factor is definitely not hydrochloric acid, though its absence is practically always associated with absence of free hydrochloric acid in the stomach contents. It is well known that this deficiency exerts its influence chiefly on the blood-forming organs and the nervous system. It is a fact, though in my opinion not uniformly appreciated by clinicians and hematologists, that these two systems may be affected concurrently or entirely independently of each other. McCann and Maitland-Jones⁴ state that the cord symptoms may be primary and predominant and may occur in pernicious anemia without other symptoms and without changes in the blood picture. The opinion of Ordway and Gorham⁵ is that the neurological signs may precede the onset of the appearance of the anemia by years. Davidson and Gulland⁶ state that cases of pure subacute combined degeneration occur in which no anemia may be present at all and many patients die from the pathological changes in the spinal cord at a time when the blood picture may be only slightly affected.

The pathogenesis of neurological involvement in pernicious anemia is not known. It is no longer considered a tenable theory that the neurological lesions are a direct result of the anemia per se since, as stated above, it may occur in cases without anemia and many patients with severe anemia present little or no evidence of neurological involvement. Davidson and Gulland believe that there is a constitutional factor in pernicious anemia, meaning that the central nervous systems of certain patients are unable to stand stress and strain to a normal degree. If true, this would explain why the neurological manifestations predominate in some and anemia in others.

The incidence of neurological involvement in pernicious anemia has been variously estimated at from 5 to 80 per cent. It seems that this discrepancy may be accounted for by a difference of opinion as to what constitutes neurological involvement. If only those cases are included in which at autopsy gross and microscopic changes can be demonstrated in the cord, perhaps 5 per cent is a fair estimate. On the other hand, if paresthesias, such as numbness and tingling of the hands and feet, are considered evidences of neurological involvement, certainly 80 per cent is not too high. It has been stated that many of the neurological manifestations are due to toxic causes and that normal function returns with the removal of these causes. Similar phenomena occur in other toxic states. For example, the positive Babinski

* Received for publication October 12, 1934

reaction in certain uremic patients becomes negative when the uremia disappears. No figures are available relative to the incidence of neurological manifestations of pernicious anemia associated with normal blood pictures.

The neurologic lesion in pernicious anemia consists chiefly of subacute combined degeneration of the cord, though in many instances the brain, and perhaps also the peripheral nerves, are involved. Grossly, the cord is enlarged, due partly to edema. Microscopically, the degeneration is seen to occur in patches which may increase in size and coalesce. These patches appear first in the white matter, generally in the posterior columns, and later in the lateral columns. Finally the gray matter is involved, but this is a result of injury to the tracts previously diseased. In the late stages, the anterior columns may also become affected. The lesion occurs first in the lower thoracic region, from which area it spreads both up and down the cord.

The neurologic manifestations vary greatly, depending upon the location and extent of the pathologic process. Paresthesias, such as numbness and tingling in the extremities, burning or coldness, formication, pain and diminished temperature sense, are the most common and usually the earliest symptoms. Ataxia with loss of sense of position and astereognosis are usually later manifestations. Diminution or loss of vibratory sense in the lower extremities is a rather constant sign. The tendon reflexes in the lower extremities are often increased early and in the later stages diminished or absent. The abdominal and cremasteric reflexes are usually diminished or absent. A positive Romberg's sign is often present and a positive Babinski's sign is less frequently so. In Woltmann's⁷ analysis of 150 cases of pernicious anemia, he found paresthesia present in 80 per cent, vibratory sense diminished or absent in 96 per cent, knee jerks increased in 39 per cent, diminished or absent in 36 per cent and unequal in 14 per cent, Achilles tendon reflex was increased in 23 per cent, diminished or absent in 67 per cent and unequal in 11 per cent, Romberg's sign was found in 52 per cent. He also found multiple neuritis in addition to evidence of spinal cord lesions in 5 per cent of cases.

As examples of patients manifesting neurologic evidences of pernicious anemia without alteration of the blood picture, the following case reports are briefly submitted, with negative and irrelevant data purposely omitted.

CASE REPORTS

Case 1 Mrs. J. L. W., 55 years of age, was first seen June 12, 1933, complaining of diarrhea, numbness and tingling of the hands and feet and weakness. The diarrhea had been present more or less continuously for several years, but had been very much worse for the preceding three or four months. It occurred chiefly from midnight to noon during which time 20 to 40 stools were passed, the frequency preventing sleep. Considerable griping, cramping and present. The stools contained much mucus, but no blood. had disclosed the absence of free hydrochloric acid in the stomach. hydrochloric acid had been taken over prolonged periods with

Numbness and tingling of the extremities, occurring in cycles, had been present for several years. Weakness was profound, rendering the patient unable to attend to any of her household duties. Moderate unsteadiness of gait had been present, chiefly noted when walking in the dark. She complained of attacks of dizziness, principally on change of position, but also sometimes when lying in bed.

General physical examination disclosed only moderate obesity and mild hypertension, the blood pressure being 170 systolic and 100 diastolic. Neurologically, the knee jerks were equal and exaggerated, the vibratory sense was markedly diminished in the lower extremities and Romberg's sign was positive. Examinations of urine and stools were negative. Gastric contents contained no free hydrochloric acid. The blood picture was normal (table 1) except for a slight leukopenia and a relative lymphocytosis. Roentgenologic examination of sinuses, chest, gall-bladder and gastrointestinal tract disclosed nothing abnormal except for very rapid emptying of the colon. Barium enema disclosed no filling defects.

TABLE I

Case	R B C	Hgb	C V	W B C	Lymph	Aniso	Poikil	M C V	M C H
I	5.1	14.5	40	5,400	52%	—	—	78	28.5
II	4.5	12.5	37	7,400	39%	—	—	82.2	27.8
III	5.0	13.5	42	7,600	25%	—	—	84	27

R B C—Red cell count in millions. Hgb—Hemoglobin in grams per 100 c c of blood. C V—Volume of packed cells per 100 c c of blood. M C V—Mean corpuscular volume (cubic microns). M C H—Mean corpuscular hemoglobin (micromicrograms).

With the administration of liver extract, the patient has remained almost entirely symptom free over a period of 15 months.

Case 2 Mrs. D. M., 38 years old, was seen on July 26, 1933, complaining of weakness, headaches, numbness below the elbows and knees, shortness of breath, nervousness and dizziness. These symptoms began five months previously, and had become progressively worse. Similar symptoms were present in 1929, continued about two months and disappeared spontaneously.

General physical examination was negative. Neurological examination disclosed exaggerated knee jerks, diminished vibratory sense and positive Romberg's sign. The blood picture was entirely normal (table 1). Gastric contents contained no free hydrochloric acid. The spinal fluid was examined and rather extensive roentgenologic studies were made, but no other abnormalities were detected.

For five months the patient was given dilute hydrochloric acid and treated more or less symptomatically, but no improvement occurred. In January 1934, liver extract was begun, followed within two weeks by almost complete amelioration of symptoms.

Case 3 Mrs. B. S. G., 47 years of age, was first seen May 7, 1934, complaining of neuritic pains over the back and liver region, digestive disturbances, profound weakness, numbness and tingling of the hands and feet, sore tongue, slight fever and slight loss of weight. Symptoms had been present about six months and had become progressively worse, but similar attacks had occurred over a period of at least 10 years. The digestive symptoms consisted of irregular appetite, nausea and vomiting stated that present at some time every day, and diarrhea.

and that normal had a glazed appearance with definite atrophy of the papillae and a phenomena occur in other parts of the edges. The knee jerks were markedly exaggerated, very much diminished and Romberg's sign was positive with right. Marked cutaneous hyperesthesia, and in areas numb-

* Received for publication.

ness to stroking, were present over the distribution of the sixth to the ninth cranial nerves on the right. The blood picture was entirely normal (table 1) and all other laboratory tests disclosed nothing abnormal except the gastric analysis, which revealed an absence of free hydrochloric acid. Roentgenologic examinations were made of the teeth, sinuses, chest, gall-bladder, gastrointestinal tract, kidneys and spine with negative results.

Relief of symptoms was prompt and gratifying after institution of liver therapy and has remained so with its continuance.

These three patients presented many symptoms and signs in common. All complained of symptoms over a prolonged period. Remissions and exacerbations were present in all. All complained of profound weakness and numbness and tingling of the hands and feet. Two complained of dizziness and unsteadiness of gait. Two had severe gastrointestinal symptoms, diarrhea being present in both cases and nausea and vomiting in one. Only one complained of sore tongue. All had an absence of free hydrochloric acid in the stomach contents, diminished vibratory sense, exaggerated knee jerks and positive Romberg's sign. One had peripheral neuritis. Two had normal blood pictures, except that one had a slight leukopenia with a slight increase in the percentage of lymphocytes. All responded symptomatically to liver extract.

It seems likely that too often pernicious anemia is not considered a possible diagnosis because there is no reduction in the number of red blood cells. Undoubtedly, the most constant single finding in pernicious anemia is achlorhydria. Any patient with an absence of free hydrochloric acid in the stomach contents, complaining of symptoms of pernicious anemia and presenting some evidences of neurological involvement characteristic of the disease, in whom no other cause of disability can be detected by thorough and careful examination, should, in my opinion, be given at least a tentative diagnosis of pernicious anemia regardless of the blood picture. He may then have the advantage of liver therapy before irreparable damage has been done to the central nervous system. Even death from subacute combined degeneration may be prevented or postponed thereby.

The effect of liver on the neurological manifestations of pernicious anemia is a subject regarding which there is considerable divergence of opinion. Minot and Murphy⁸ stated that neural symptoms in pernicious anemia responded less completely and less readily to treatment than other accompanying conditions. Davidson and Gulland⁹ sound a rather pessimistic note and seem inclined to attribute the subjective improvement when it occurs, to the effect on the nervous system of the improvement in muscular tone, in the anemia and in the general condition of the patient. Some authors even state that there is a progression of the cord degeneration in spite of and during the administration of liver. On the other hand, those who have noted subsidence of the degenerative process with improvement or complete relief of symptoms are too numerous to attribute to mere coincidence or optimism. Tenney and Goldstein¹⁰ have reported a case

pernicious anemia with psychoneurotic symptoms antedating the development of the anemia by many years in which there was lasting and rapid recession of mental symptoms with the administration of liver extract Ungley and Suzman¹⁰ reported 61 cases of pernicious anemia with neurological involvement, 30 of whom received adequate liver therapy Of these 30, five died, eight failed to improve or became worse and 17 improved The improvement in some of these was sufficiently marked to enable them to resume work in the ship-building yards, whereas, previous to treatment, they had been bed-ridden Of the 31 cases who received no treatment, 28 died and the remaining three either failed to improve or became worse Garvey, Levin and Guller,¹¹ from a series of 47 patients, concluded that liver therapy relieved the neurologic symptoms, but had no effect on the neurologic objective signs Obviously, we can not expect liver or any other known substance to replace neurones which have already undergone degeneration However, as has been pointed out, many of the symptoms and some of the signs of neurologic involvement are probably toxic in origin and may disappear if the cause be removed It appears safe to say that the majority of investigators agree that improvement in neurologic symptoms occurs in most cases and that progression of the degenerative process takes place in very few with adequate liver therapy This is one of the chief arguments in favor of the necessity for early diagnosis In my own small series of cases of pernicious anemia, liver therapy has not failed in a single instance to produce improvement in neurologic symptoms This applies in equal measure to those cases of neurologic involvement without anemia and those with an associated anemia

SUMMARY

- 1 The causative factor in pernicious anemia affects chiefly the nervous system and the blood-forming organs These may be involved concurrently, or either may be affected independently of the other
- 2 The pathogenesis and pathology of neurological involvement are briefly discussed and the symptoms and signs reviewed
- 3 Three cases of pernicious anemia with neurological involvement and with normal blood pictures are reported All responded well to liver extract
- 4 The effect of liver therapy on the central nervous system involvement in pernicious anemia is discussed and a plea made for early diagnosis and treatment

REFERENCES

- 1 CASTLE, W B Observations on the etiologic relationship of achylia gastrica to pernicious anemia, *Am Jr Med Sci*, 1929, clxxviii, 748-764
- 2 CASTLE, W B, and TOWNSEND, W C Observations on the etiologic relationship of achylia to pernicious anemia, *Am Jr Med Sci*, 1929, clxxviii, 764-777
- 3 CASTLE, W B, HATH, C W, and STRAUSS, M B Observations on the etiologic relationship of achylia gastrica to pernicious anemia, *Am Jr Med Sci*, 1931, clxxxii, 741-764
- 4 MCCANN, W S, and MAITLAND-JONES, A G Text-book of medicine, Cecil, 1928, W B Saunders Co., Philadelphia

- 5 ORDWAY, T, and GORHAM, L W Oxford monograph on diagnosis and treatment of diseases of the blood, Oxford University Press, 1930, ix, 65
- 6 DAVIDSON, L S P, and GULLAND, G L Pernicious anemia, 1930, C V Mosby Co, St Louis
- 7 WOLTMANN, H W The nervous symptoms in pernicious anemia, a analysis of 150 cases, Am Jr Med Sci, 1919, clvii, 400
- 8 MINOT, G R, and MURPHY, W P A diet rich in liver in the treatment of pernicious anemia, Jr Am Med Assoc, 1927, lxxviii, 759-766
- 9 TENNEY, C F, and GOLDSTEIN, E The mental symptoms of pernicious anemia and their response to liver therapy, Med Clin N Am, 1933, xvii, 185-191
- 10 UNGLEY, C C, and SUZMAN, M W Subacute combined degeneration of the cord symptomatology and effects of liver therapy, Brain, 1929, lii, 271-294
- 11 GARVEY, P H, LEVIN, P M, and GULLER, E I The effect of liver therapy on the neurologic aspects of pernicious anemia, ANN INT MED, 1933, vi, 1441-1448

CASE REPORTS

DINITROPHENOL AND RAPIDLY DEVELOPING CATARACTS

By W W BOARDMAN, M D, F A C P, *San Francisco, California*

CHRONIC obesity decreases efficiency and shortens life expectancy, especially through the increased incidence of cardiovascular disease and diabetes. The control of chronic obesity is therefore a definite and important problem in preventive medicine. Much has been written regarding the cause or causes of chronic obesity but, in the final analysis, obesity results from an excess of energy intake over the energy demands of the body. The control of obesity must lie in a reversal of this relationship with the creation of a deficit on the side of the intake as compared with the expenditure of energy.

To obtain this result, three methods are available: (1) to decrease the energy intake, (2) to increase the energy demands, (3) to combine both procedures. In a large percentage, the obesity is obviously exogenous, due to excessive food intake, and these cases respond readily to moderate dietary restrictions, if faithfully persevered in. There is a second group, the so-called endogenous cases, in which the obesity results more from a disturbed metabolism with decreased energy demands than from an excessive food intake. Some of these cases are associated with well-recognized endocrine disturbances, such as thyroid or pituitary, others, however, cannot be connected with any as yet known endocrine disturbance.

In both groups, but especially in the latter, it is frequently necessary to reduce the caloric intake to such a low point that the patient becomes discouraged and gives up all effort at dietary control. In properly selected cases, satisfactory results are frequently obtained by supplementing the dietary restrictions with various endocrine preparations. There still remains a large group in which the results are unsatisfactory, either because of failure on the part of the patient to decrease the caloric intake, or because of failure of the endocrine preparations or other procedures sufficiently to increase the energy demands.

There is obviously a place for a safe metabolic stimulant that can be administered by mouth and that is free from the unpleasant symptoms, inconvenience, and expense attendant upon the use of the present endocrine preparations. This want seemed to have been satisfied when Cutting, Mehrtens, and Tainter reported on their studies of dinitrophenol in 1933. Here was a drug capable of markedly stimulating the metabolic rate, after exhaustive animal and careful clinical study apparently free from serious deleterious effect upon the human organism when given in proper dosage, and, finally, effectual on oral administration. In some cases it caused skin irritation which, however, promptly cleared on discontinuing the drug. A few adverse reports appeared but these were explained on the basis of coincidence, excessive dosage, or unusual idiosyncrasy.

The drug rapidly gained wide acceptance, both with the profession and with the laity. Because of its marked potency and the occurrence of several fatal cases from overdosage either accidentally or intentionally self-administered, in

* Received for publication June 24, 1935

California dinitrophenol was placed on the list of dangerous drugs and could be sold only on the physician's prescription. However, as reported by Dr. Geiger, even when taken in marked excess a fatal termination could be prevented by immersing the patient in a cold bath. The drug was studied and used extensively, both here and abroad, and although the very conservative were inclined to await the verdict of time before adopting it, it was generally believed that under controlled conditions, dinitrophenol was free from danger, and that, combined with dietary restrictions, it was of definite value in obtaining weight loss in refractory cases under ambulatory conditions. It proved of especial value in producing a prompt drop in weight, so encouraging the patient to persist more faithfully in the dietary restrictions. Strang and Evans in a recent study, although advising against its continued use state that "no symptoms other than cutaneous were noted that could consistently be attributed to the use of the drug."

Thus matters stood until about the middle of May when a case that had been under treatment by Dr. R. B. Jones complained of dimness of vision and was found to have cataracts.

CASE REPORTS

Case 1 Mrs. L., aged 50, was started on sodium dinitrophenol October 20, 1933, beginning with 100 mg. per day and gradually increasing to 500 mg. per day for a total dosage of 780 one-hundred milligram capsules and a total weight loss of 49 pounds, going from 237½ to 188½ pounds. The drug was discontinued from March 5, 1934 to May 17, 1934. A second course was given from May 17, 1934 to July 19 for a total weight loss of 17 pounds and a total dosage of 229 one-hundred milligram capsules. The patient maintained her weight at approximately 160 pounds until April 18, 1935 when, with a weight of 164, dinitrophenol was again administered with 200 mg. per day for one week, 300 mg. per day the second week, and finally 400 mg. per day. At this point, dimness of vision was complained of and incipient cataracts were found. The lens opacification increased rapidly, vision was reduced from 08 to hand movements at three feet in slightly over one month, and this patient is now awaiting cataract extraction. This patient had received a total of 1072 one-hundred milligram capsules over a period of 18 months.

This case was discussed with Dr. M. L. Tamter who had seen a similar case treated by Dr. A. B. Stockton.

Case 2 A woman, aged 39, had been given dinitrophenol interruptedly over a period of eight or nine months with satisfactory weight reduction. In November 1934, she reported that her vision was getting dim and within 30 days this had progressed to almost complete blindness, and with fully developed cataracts. This patient was operated upon by Dr. Hans Barkan.

With these two cases occurring in relatively young women, although there was no clear evidence that dinitrophenol was responsible, it was impossible to avoid suspicion that in some way the drug was implicated. This suspicion was strengthened when the following case was reported.

Case 3 Mrs. A., aged 36, was treated continuously from January 20, 1934 to July 24, 1934 with a maximum dosage of 500 mg. per day, a total dosage of 910 one-hundred milligram capsules, and a total weight loss of 66½ pounds, going from 222½ to 156 pounds. There was then a period of seven months without dinitrophenol and failure to follow dietary instructions with a resulting gain in weight of 44 pounds. The dinitrophenol was again administered on March 13, gradually increasing to a

maximum dosage of 400 mg per day for a total dosage of 231 one-hundred milligram capsules and a total weight loss of 12 pounds. The drug was discontinued on May 14 because of the finding of incipient cataracts in both eyes. This patient had a total of 1141 one-hundred milligram capsules of dinitrophenol over a period of 16 months. The opacification progressed rapidly in the right eye so that lens extraction will be necessary. The process has not progressed during three weeks' observation of the left eye.

At this point, three cases of cataract developing in relatively young women who had been taking dinitrophenol were reported by Oakland physicians.

Cases 4, 5 and 6 A woman, about 40 years of age, reported by Dr. J. R. Sharpsteen of Oakland, had been taking dinitrophenol without a physician's supervision for several months. She also has shown rapidly developing cataracts.

Two other cases, reported by Oakland physicians, of rapidly developing cataracts in women who have been taking dinitrophenol.

Routine eye examinations were now made on several cases that had been taking dinitrophenol with the result that out of about 12 cases one other case showed slight changes.

Case 7 Mrs. P., aged 39, started on sodium dinitrophenol March 1, 1934, beginning with 100 mg per day and gradually increasing to a maximum of 500 mg per day for a total of 316 one-hundred milligram capsules and a total weight loss of 21¼ pounds. The drug was discontinued from June 26, 1934, but with this relatively short period of treatment and small total dosage, definite but slight lens changes are evident one year later.

Another case recently appeared.

Case 8 Mrs. H., aged 44, took sodium dinitrophenol from November 23, 1933 to April 30, 1934, gradually increasing to a maximum of 500 mg per day and for a total dosage of approximately 650 one-hundred mg capsules and a total weight loss of 26 pounds. No dinitrophenol was given after April 1934 but for some months, dimness of vision has been complained of and in June 1935 well-developed cataracts were found.

In all of these cases occurring in relatively young women showing certain unusual and apparently characteristic lens changes and usually progressing rapidly to complete cataract, the only common factors have been dietary restriction and the administration of dinitrophenol. Of course, this association does not prove dinitrophenol the causative agent, but it certainly does indicate that until this entire question is clarified, dinitrophenol must not be administered.

Many questions arise as to why, if dinitrophenol is the causative agent, it has taken 18 months for the signs and symptoms to appear, why, in some, no symptoms have appeared for over a year after discontinuing the drug while in others symptoms developed in a few months, is the action a direct toxic effect on the lens or indirect through some metabolic change, and is the change associated with the size of the daily dose or the total dosage?

These and many more questions demand study and explanation but the answers can wait. At present, the important indication is to discontinue the use of dinitrophenol.

TOXIC REACTION TO ALPHA-DINITRO-ORTHO-CRESOL

By MURRAY B GORDON, M D , F A C P , and MARK J WALLFIELD, M D ,
Brooklyn, New York

THE use of the nitrophenol group as a metabolic stimulant has brought to light many reports of toxic reactions^{1,2,3,4} and even fatalities⁵. Cutting, Mehlens and Tainter² have sounded a sombre note of warning that the drug is still too new in usage and the various manifestations of toxicity are not known. More recently, Dodds and Pope⁶ have reported better results in the treatment of obesity with the use of dinitro-ortho-cresol instead of dinitrophenol. The clinical application of the drug by Dodds and Robertson⁷ has shown it to be from three to five times as strong as dinitrophenol, yet apparently of the same toxicity. The dosage advocated by them was from 50 to 100 mg per day for a normal adult person. As a further check, the basal metabolic rate should never be allowed to exceed plus 50.

We have found no clinical report of a reaction to dinitro-ortho-cresol in the literature, and deemed it of interest to record the findings in our case.

CASE REPORT

P F, white female, age 14½ years, was admitted to the endocrine clinic in January 1933 for treatment of obesity. A diagnosis of pituitary obesity with secondary hypothyroidism was made, and treatment consisting of thyroid and pituitary extract orally and hypodermic injections of anterior pituitary solution was instituted. She responded well to this therapy together with a high protein, low fat and carbohydrate diet for about six months, lost 14 pounds and grew 2½ inches. During the second half of 1933 she was somewhat lax in her attendance at the clinic and in her diet, and her weight rose from 110 to 122 pounds. In January 1934 she gained rapidly, and did not respond to the former diet and medications. It was decided to use alpha-dinitro-ortho-cresol^{3,4,5} as a metabolic stimulant, and this was started on April 4, 1934. No other medication was given and her former diet was continued. Her weight at that time was 132 pounds (60 kg), and a dose of one capsule of 100 mg of dinitro-ortho-cresol daily was ordered for one week. As there was no resultant loss in weight, the dose was increased to two capsules a day. On April 15, after four days of the increased dosage, the patient awoke, complained of feeling drowsy, and noted a swelling of the fingers and hands. It was found necessary to remove a school ring from the finger because of the swelling. During the day a greenish-yellow color of the sclerae was observed, and the urine was reported to be extremely dark and odorous.

The next day, Monday, April 16, the patient went to school against advice, but was so drowsy that she fell asleep in the classroom. A headache was present at this time and an itching maculo-papular eruption appeared during the afternoon. That night she was nauseated and vomited several times. In spite of the malaise, she again went to school the following morning, but returned home because of drowsiness, headache, nausea and a ringing sensation in the head which was exaggerated on climbing stairs.

The medication had been discontinued as soon as this train of symptoms set in, but the patient did not return to the clinic until April 18, four days later. The total amount of the drug taken was 15 capsules of 100 mg each, or 15 gm of dinitro-

* Received for publication September 14, 1934

From the Endocrine Clinic, Israel-Zion Hospital, Brooklyn, N Y

ortho-cresol over a period of 11 days. Physical examination on April 18 revealed a marked icterus of the sclerae, but not of the skin or mucous membrane of the mouth. The pulse rate was 90 per minute, of good volume and normal rhythm. The heart and lungs were normal, there was no liver enlargement or any hepatic tenderness. The general condition was good, no skin rash was present, and there were no other complaints.

Laboratory Examinations Urine was dark in color, had a strong odor, showed a faint trace of albumin, bile pigment was absent.

Blood count: red blood cells, 4,300,000, hemoglobin, 80 per cent (Sahl), white cells, 6,600, polymorphonuclears, 55 per cent, lymphocytes, 35 per cent, mononuclears, 5 per cent, eosinophiles, 5 per cent. Platelets, 200,000. Bleeding time, 8½ minutes, coagulation time 9 minutes.

Blood chemistry (mg per 100 c.c.) glucose 92.7, urea nitrogen 14.8, non-protein nitrogen 27.4, creatinine 1.52, uric acid 3.52, cholesterol 178, chlorides—whole blood 469.7, plasma 592.3, red cells 284.2.

Icteric index 24.75. Van den Bergh reaction negative in both direct and indirect phases.

Reexamination of the patient one week later, April 25, showed a diminution in the yellow discoloration of the sclerae and urine. There was no loss of weight during this period. On the thirteenth day after the onset of symptoms, the swelling of the fingers and hands recurred, and lasted for an additional 48 hours.

Treatment consisted of local application of calamine and zinc lotion for the rash, and general purgation to hasten excretion of the drug. It was later ascertained that the patient had been eating considerable amounts of candy every day, merely as a whim, and not because of hunger.

COMMENT

Unfortunately we were unable to obtain a basal metabolic rate on our patient during the acute stage, and to report any later reading would be but fallacious. Of extreme interest are the following features: the greenish-yellow color of the sclerae and no signs of jaundice of the skin or mucous membranes, the extremely dark colored urine showing a negative bile test, and lastly, an icteric index of 24.75 and a negative Van den Bergh reaction, indicating no true hepatic involvement. This clinical picture of "jaundice" is accounted for by the yellow color of the drug itself in solution, and is not astounding when one recalls the deep yellow color of picric acid solution (trinitrophenol), and the close chemical relationship of dinitrocresol to it. The yellow discoloration of the drug in the blood serum can be removed by adding a few drops of a 5 per cent solution of HCl, as advised by Tainter and his co-workers. Isaacs⁹ reported such a revised icteric index reading of 5.3 instead of the original one of 20 in Jackson's¹ case of dinitrophenol poisoning. The same chemical reaction holds true for dinitro-ortho-cresol.

SUMMARY

A case of a toxic reaction to alpha-dinitro-ortho-cresol^{3,5} is reported in a girl 14½ years of age. The symptoms manifested were marked drowsiness, headache, nausea, vomiting, swelling of the fingers and hands, an itching maculopapular rash, yellow colored sclerae and a dark urine. The icteric index was 24.75 (not decolorized) and the Van den Bergh reaction was negative.

BIBLIOGRAPHY

- 1 JACKSON, H, and DUVALL, A I Dinitrophenol poisoning, Jr Am Med Assoc, 1934, cii, 1844-1845
- 2 CUTTING, W C, MEHRTLINS, H G, and TAINTER, M L Actions and uscs of dinitrophenol, Jr Am Med Assoc, 1933, ci, 193-195
- 3 CUTTING, W C, and TAINTER, M L Metabolic actions of dinitrophenol, 1933, ci, 2099-2102
- 4 ANDERSON, H H, REED, A C, and EMEKSON, G A Toxicity of alpha-dinitrophenol, Jr Am Med Assoc, 1933, ci, 1053-1055
- 5 GEIGER, J C Death from alpha-dinitrophenol poisoning, Jr Am Med Assoc, 1933, ci, 1333
- 6 DODDS, E C, and POPE, W J Dinitro-o-cresol as stimulator of metabolism, Lancet, 1933, ii, 352-353
- 7 DODDS, E C, and ROBERTSON, J D Clinical applications of dinitro-o-cresol, Lancet, 1933, ii, 1137-1139
- 8 TAINTER, M L, STOCKTON, A B, and CUTTING, W C Use of dinitrophenol in obesity and related conditions, Jr Am Med Assoc, 1933, ci, 1472-1475
- 9 ISAACS, B L Dinitrophenol poisoning, Jr Am Med Assoc, 1934, cii, 2218

PRIMARY COSTAL OSTEOMYELITIS ¹

REPORT OF A CASE

By HAROLD R ROEHM, M S, M D, *Birmingham, Michigan*

PRIMARY osteomyelitis of the ribs in children is not a common condition in this country judging from reports to be found in the literature Farr ¹ reported five cases in a series of 98 patients with osteomyelitis, and Phemister ² three in a series of 320 cases

Ameline,³ and Parcelier and Chauvenet ⁴ give credit to Jaboulay for the first description of the disease in 1885, and to Lannelongue for the second published report in 1890 Since the first report Ameline has found in European literature reports of approximately 100 cases in patients of all ages

Secondary osteomyelitis of ribs is more common Andieson ⁵ reported a case in a seven weeks old infant following an upper respiratory infection Gamboa and Montarce ⁶ reported a case of costal and vertebral osteomyelitis in a 40 day old infant following traumatism of the right hip Coursieres ⁷ reported a case in an infant following typhoid fever Ameline has found that costal osteomyelitis may follow eruptive fevers particularly varicella, typhus, recurrent, and Malta fevers, and septicemias Philardeau ⁸ reported a case in a four and a half year old child following varicella In their review of 92 cases, Parcelier and Chauvenet found that bacteriologic examination was made in 32 cases and of these 20 were caused by staphylococci, eight by streptococci, two by pneumococci and one each by a diplococcus and an enterococcus

Wolf and Ring ⁹ report one case following otitis media and an evident streptococcic septicemia in a six months old infant

The diagnosis of costal osteomyelitis is at times difficult to make particularly

* Received for publication September 22 1934

From the Pediatric Division, St Joseph's Mercy Hospital, Pontiac, Michigan

when the posterior portion of an upper rib is involved or the picture is complicated by an empyema. In cases with localized swelling, redness, and tenderness, the diagnosis is more obvious. In cases in which the posterior portion of a rib is involved and in which tenderness and muscle spasm are the only signs, and fever and pain the only symptoms, the clarity of the picture is obscured and one may be left in doubt until secondary manifestations of the infection appear. Roentgen-ray may be of only negative assistance as in the case to be presented.

The treatment advocated by all authors quoted above, except Wolf, is resection of the diseased portion of the rib. Graham¹⁰ reported a complete recovery from a draining sinus following a primary staphylococcal costal osteomyelitis after operation and removal of a sequestrum. Kelley¹¹ describing variant types of osteomyelitis writes that in mild, subacute, or serous osteomyelitis, operation should be immediate, though in this type, and in typhoidal osteomyelitis the surgical intervention is not usually so extensive as in the acute fulminating types.

The prognosis of acute costal osteomyelitis is probably similar to that of osteomyelitis elsewhere. DaCosta¹² taking his statistics from Kennedy gives a general mortality of 34 per cent for all osteomyelitis, and 10 per cent for those cases operated upon within 44 hours of the initial chill. Ameline in reviewing 96 cases of costal osteomyelitis found a mortality of 9.6 per cent.

In the case to be described here, the course and resolution of the disease presented unusual features.

CASE REPORT

The patient, a nine year old boy, was first seen because of his present illness on June 21, 1933. The mother stated that for about a week he had complained of pain in the region of the right scapula and had had a low fever. There was no history of injury or previous illness in the past year with the exception of varicella six months before. On examination there was moderate tenderness over the fifth right rib posteriorly four inches (10 cm.) from the spine, with some muscle spasm. There was no redness or swelling. His rectal temperature was 101° F. There was no cough, no pain during respiration, nor were any abnormal breath sounds heard. Salicylates were prescribed, and the mother was requested to report her observations of the child's temperature. One week later the child was again seen, and at this time the area of tenderness of the right chest posteriorly was more marked, involving the fourth, fifth, and sixth ribs. The rectal temperature was 102° F and the respiratory movements of the right chest were somewhat limited. The boy appeared to be more ill than when previously seen. The evening of the twenty-ninth, his temperature went to 105° F and the following morning the child was sent to the hospital. Stereo roentgenograms were taken of the chest both for bone detail (figure 1) and soft tissues. The ribs appeared normal but there was a pleurisy and early pneumonic infiltration of the upper lobe of the right lung. The white blood cell count at this time was 16,000, of which 82 per cent were polymorphonuclear neutrophils, and of these 17 per cent were eosinophils. This large number of eosinophils is interesting in view of the fact that 48 hours later the patient developed a severe generalized urticaria. A Mantoux tuberculin test with 0.1 mg. OT was negative. Following the appearance of the urticaria the temperature dropped to normal and the boy felt quite well except for complaints of pain on movement of the right arm and the neck. The following day the patient began to cough and the temperature in the next 24 hours mounted to 105.8° F. Another roentgen-ray was taken on July 5, the sixth hospital day. This showed a uniform opacity over the entire right chest indicating a definite

pleural effusion The next day, July 6, thoracentesis was done and 150 c c of a slightly cloudy, yellow fluid were obtained, which when cultured produced a pure growth of hemolytic *Staphylococcus aureus* The course of the patient's illness was quite stormy at this time, the temperature varying between 98° and 104° F, the boy complaining of great pain in the right chest and a severe urticaria coming and going intermittently An intradermal injection of a suspension of the killed staphylococcus containing six billion bacteria per c c, obtained from culture of the pleural exudate produced a wheal 1 cm in diameter surrounded by an area of erythema 6 cm in



FIG 1 Early pneumonic infiltration of the upper lobe of the right lung No evidence of rib involvement



FIG 2 Osteomyelitis of the posterior portion of the fifth right rib. Catheter draining the empyema may be seen at the lower left.

diameter. The right pleural cavity was again aspirated on July 8, the ninth hospital day, and 115 cc of exudate removed. On July 10, a catheter was inserted in the pleural cavity between the seventh and eighth ribs in the right posterior axillary line for continuous closed drainage. The pleural cavity was irrigated with normal saline two or three times daily. For five days following the institution of continuous drainage the boy complained of such severe pain in the right chest that codeine was

necessary to control it, although his temperature had not risen above 100.8°F . After this time he seemed much more comfortable, his appetite improved, and his temperature varied from 99° to 100°F . On July 31, the thirty-second hospital day, another roentgen-ray (figure 2) was taken to check the progress of the empyema

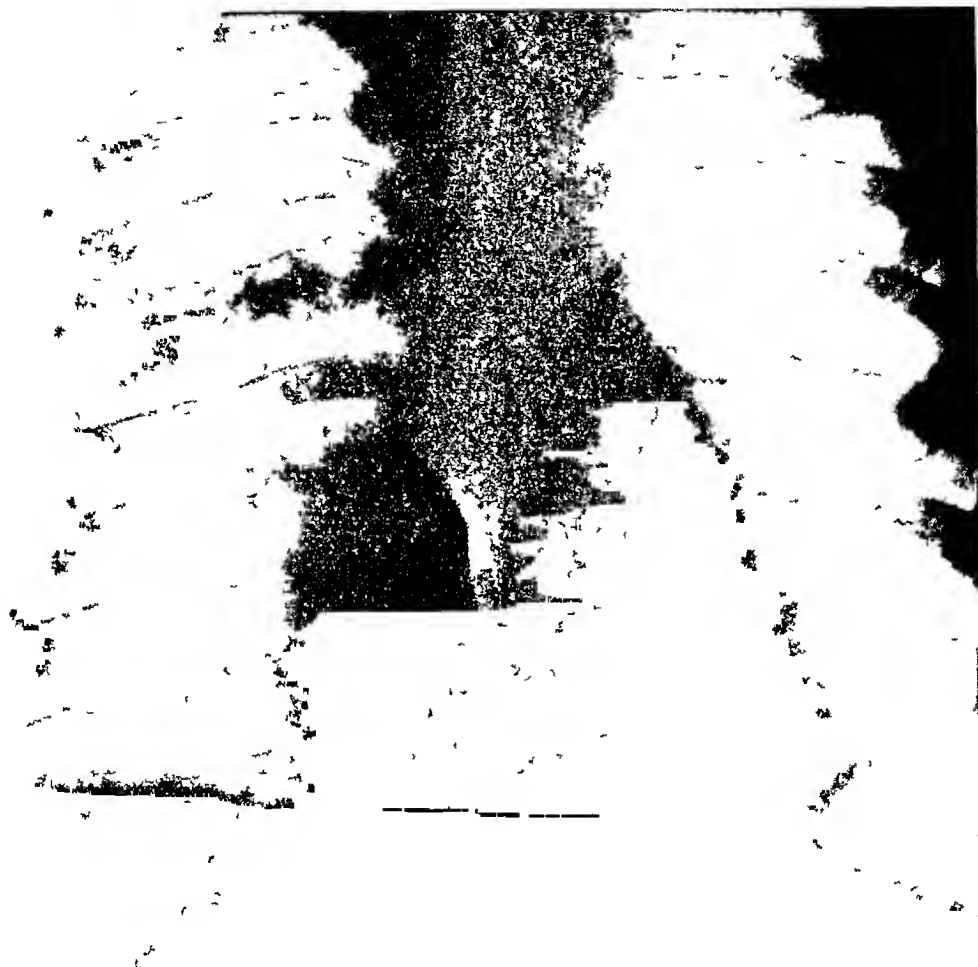


FIG 3 Healed costal osteomyelitis two and one-half months after onset of the disease

This showed the pleural cavity to be almost free of fluid and also showed an evident osteomyelitis of the posterior third of the right fifth rib. Because of the clinical improvement manifested by the child and because it seemed reasonable to believe that drainage from the involved rib was occurring through the pleural cavity, it

was felt justifiable to withhold surgical interference until further observations had been made. A roentgen-ray taken 10 days later showed no extension of the process in the rib and there appeared to be some indication of new bone formation along its superior surface. The drainage tube was removed at this time, one month after its

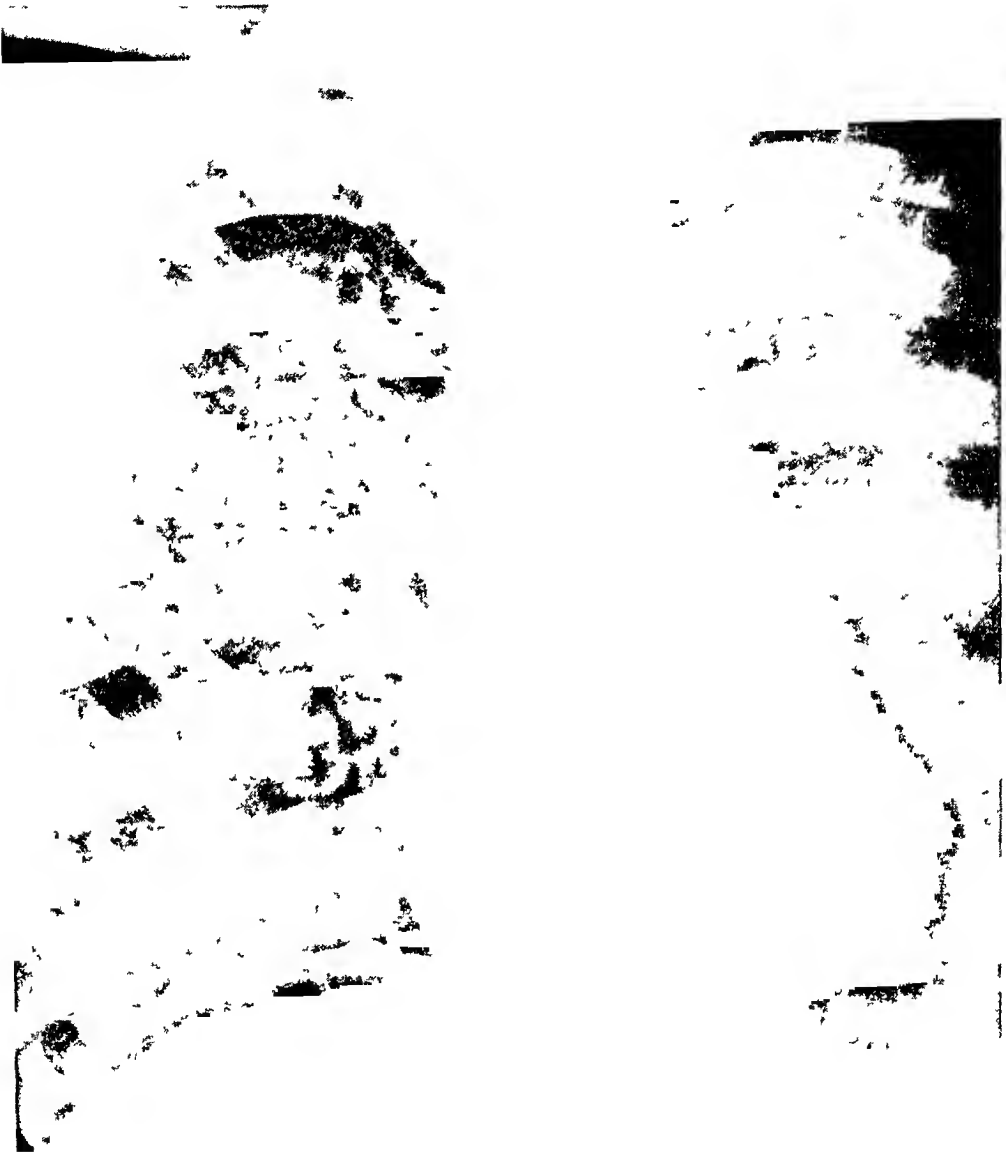


FIG 4 Healed costal osteomyelitis 15 months after onset of the disease

insertion and on the forty-second hospital day. The boy continued to improve and was discharged cured, August 15, after a hospital stay of 48 days. This patient was carefully followed after leaving the hospital and roentgen-rays (figures 3 and 4) were

taken monthly until February 1934, six months after his discharge. These showed progressive filling of the bone defect caused by the osteomyelitis. The boy was examined in July 1934, one year after the onset of his illness and showed at this time a symmetrical chest without visible defects, with no evidence of any activity at the site of his previous costal osteomyelitis.

SUMMARY

A case of osteomyelitis of the posterior third of the fifth right rib is presented which healed without operation, after drainage of the accompanying empyema. Drainage from the infected rib occurred apparently into the pleural cavity contrary to the usual statement in the literature that this does not occur. Wolf has lately reported a similar experience.

The etiologic agent of the infection was a hemolytic *Staphylococcus aureus* to which the patient was sensitized and which produced a severe generalized urticaria.

The first symptoms of primary costal osteomyelitis of the posterior portion of the fifth rib are fever and localized pain. The first signs are local tenderness, muscle spasm, and pleural thickening accompanied by a rapidly developing empyema. Roentgen-ray evidence of infection may not be present until after the empyema develops. Drainage of the osteomyelitis can and does occur into the pleural cavity with spontaneous resolution of the diseased rib.

Note. Dr. Howard Barker, M.D., F.A.C.S., of the Surgical Division, instituted and supervised the drainage of the empyema in the case presented. His assistance is gratefully acknowledged.

BIBLIOGRAPHY

- 1 FARR, C. E. Acute osteomyelitis in children, *Ann Surg*, 1926, **lxxviii**, 686-692.
- 2 PHEMISTER, D. B. Unusual forms of osteomyelitis, *Northwest Med*, 1928, **xxvii**, 460-466.
- 3 AMFLINE, A. L'osteomyélite aigue primitive des côtes, *Arch med-chir de l'app respir*, 1929, **iv**, 348-355.
- 4 PARCFLIER, A., and CHAUVENET, A. L'osteomyélite primitive des côtes, *Rev de chir*, 1924, **lxii**, 671-688.
- 5 ANDERSON, O. Ein Fall von Hautempysem nach Rippenosteomyelitis bei einem jungen Säugling, *Jahrb f Kinderh*, 1932, **cxlv**, 335-340.
- 6 GAMBOA, M., and MONTARCI, H. L. Osteomyelitis vertebral y costal en un lactante, *Arch argent de pediat*, 1932, **iii**, 178-189.
- 7 COURSIER, H. De l'osteomyélite costale post-typhique, *Progres med*, 1932, 1549-1559.
- 8 PHILARDEAU, P. Contribution a l'étude de l'osteomyélite. Un cas d'osteomyélite varicellique, *Rev d'orthop*, 1922, **ix**, 233-240.
- 9 WOLF, I. J., and RING, H. B. Osteomyelitis of rib complicated by empyema in infant, *Jr Am Med Assoc*, 1934, **cii**, 2181-2182.
- 10 GRAHAM, E. A. Surgery of the thorax, *Abts Pediatrics*, 1924, Vol 4, Chapter 66, W. B. Saunders Co., Philadelphia, p 71-72.
- 11 KELLER, S. W. Surgical diseases of children, 3 Ed, Vol 1, 1929, C. V. Mosby, St. Louis, p 341-342.
- 12 DACOSTA, J. C. Modern surgery, 8 Ed, 1920, W. B. Saunders Co., Philadelphia, p 578.

EDITORIAL

OUT-PATIENT CLINIC PROBLEMS OF TODAY

THE character of dispensary work in many cities has changed radically since the inauguration of the Federal program of medical relief. It was provided in that program that medical care in the home and in the physician's office could be paid for from relief funds, but that existing medical institutions such as dispensaries were not to share in these funds but were to continue as a charge upon the private philanthropy or the local tax funds of the community. The effect of these rulings varied in different parts of the country. In some cities the major part of the medical care of the indigent on the relief rolls was undertaken by the general practitioners and there was no increase and perhaps even a decrease in dispensary attendance. In other communities a policy radically opposed to this was adopted. To conserve relief funds all of the "clients" of the relief administration were herded into the dispensaries or onto hospital wards when in need of medical care, and the provisions in the Federal regulations for their medical care in the home and for the payment of their attending physicians were ignored. Apparently neither plan has proved wholly satisfactory to the interested parties, i.e. the relief administrators, the medical institutions, the physicians and the sick people on relief. From these experiences, however, it should be possible to derive some information of interest.

In those cities in which the major part of the medical care of the indigent has been carried out by the general practitioner and has been paid from relief funds there has grown up, at least in the minds of the relief administrators, a realization of the cost of medical care and of the difficulties that arise in avoiding abuses in its administration. In those cities which have attempted to unload the whole problem upon existing medical institutions it has become apparent that such institutions cannot replace the general practitioner. It is perhaps in this last connection that the most instructive lessons concerning dispensaries and their proper functions have been learned.

It has become evident, for example, that a dispensary is no longer a dispensary, and that its adoption of a more modern name, "out-patient clinic," really corresponds to a very fundamental change in its nature. Old-fashioned dispensaries, places of snap-shot diagnosis and pill therapy, would have had less difficulty in handling the swarm of relief cases than the more modern out-patient departments. The majority of their admissions they would have turned away with a clap on the shoulder and an aspirin tablet, a compound cathartic pill or a tonic. Only a few would have been carefully examined. But modern standards in out-patient clinics necessitated a complete history and physical examination on each admission, and at least a urine test, with perhaps a Wassermann test, a blood count and in cases of doubt roentgen-rays and consultations in special clinics. All this was splen-

did but it was not war, and these were like war conditions. Where no adaptations were made the machinery clogged, overworked and disgusted doctors resigned, and the net end result was that the clinic either refused to take more than a given number of relief cases and thereby failed the community, or it disintegrated entirely. In some cities there has been quite a mortality among the smaller dispensaries. The lesson would seem to be that the modern out-patient clinic is not fitted to do general practice. It is a highly organized diagnostic and therapeutic institute for ambulant cases and it holds its volunteer staff together only in proportion to its ability to maintain standards of work which will satisfy the desires of that staff to learn more than they can learn in their own offices. If the emergencies of the present social situation force such an institution into the mass care of large groups of people presenting chiefly minor and simple problems its only salvation lies in adapting its machinery to the new demands. It may be helpful to establish an adequate admitting system which will divert into a Clinic for Minor Illness those cases which do not require the full routine of the major departments. Such a solution is not ideal but it meets the emergency far better than an "appointment system" which turns away many with no care at all, and is apt to admit today a case of chronic constipation while putting off until next week a case of juvenile diabetes.

The physicians in out-patient clinics have suffered not only because of the excessive number of cases admitted, and because so many of these cases presented only minor disorders, but also because they have had to settle problems of a type which distressed and did not interest them. Too often after a history of vague complaints had been recorded and an essentially negative physical examination performed the real purpose of the visit to the clinic was found to be in a desire to be furnished with a certificate of physical inability to work, which might be useful when a "work project" was threatening. The older physician feels that it was one thing, back in the days when he was in the army, to mark a malingerer "duty" at sick call, but another thing to be forced into the uniform of the relief administration and driven to passing judgment upon the indigent when his purpose in coming to the clinic was to aid the sick and to perfect himself in his art. The result of his distaste for the task is probably that he is over-lenient or over-severe—and that he comes a little later on his next day. Such problems of a medical administrative character might well be handled outside of the out-patient clinics by an Examining Board. The clinic should receive only the doubtful cases referred to it for more complete study.

It does not seem probable that the near future will see any marked falling off in out-patient clinic attendance. The shrinkage of Federal funds for relief those cities which have to Ed, Vol. 13, No. 1, 1933, p. 10. The free clinics, and those which have already pursued this method will be forced to continue it. It is true that the number of indigents on the relief rolls will diminish as the long heralded "Work Program" comes into effect but it is equally true that the

scale of wages paid under that program will not furnish the recipients with the means of paying physicians. We shall be seeing them in our clinics next winter. *Plus ça change, plus c'est la même chose*

The majority of internists are or have been connected with out-patient clinics. In our various communities we should now lend our counsel in the making of plans which will best adapt the out-patient clinic to the role it is called on to play.

REVIEWS

The Practitioner's Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M A (Yale), M D, F A C P, David P Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital *Volume VIII Therapeutics* Associate Editor, ALBERT I SULLIVAN, B S, M D, Assistant Professor of Medicine, Yale University School of Medicine xlv + 1031 pages, 27 illustrations D Appleton-Century Company, New York 1935 Price, \$10 00 a volume

In *Therapeutics*, more than in any other field of medicine, the practitioner has need of a comprehensive, adequately indexed textbook which will give him the well-considered opinions of experts in the management of the various diseases which he may encounter. In the treatment of the more common affections the practitioner of long experience becomes an expert himself, but for the management of the unusual condition he must turn to the advice of others. Thus, whether it be for the student or for the seasoned veteran, such a work as Volume VIII of *The Practitioner's Library* becomes a necessity. This volume, to which there are 35 contributors, combines a presentation of the principles and technic of therapeutics with a consideration of the management of the individual diseases. Part I, which is approximately one-fourth of the book, is devoted to General Therapeutics, Part II, to Special Therapeutics. In the latter the arrangement of subjects is in part etiological and in part anatomical. In the former, dietary, physical and psychotherapeutic, as well as medicinal, measures are considered.

As has been stated in the reviews of the preceding volumes of this series, it is impossible to list the individual contributors or to evaluate the separate chapters. In general, the discussions are characterized by a degree of completeness which indicates liberal space allowances from the publishers. Great care has been taken to assign the topics to recognized experts in the particular fields. This volume could deservedly stand alone as a comprehensive system of therapeutics even if it were not supported by its fellows in the Practitioner's Library.

C V W

Dietetics for the Clinician By M A BRIDGES, B S, M D, F A C P Second Edition 970 pages, 16 × 24 cm Lea and Febiger, Philadelphia 1935 Price, \$10 00

This is an ambitious treatise and a number of the sections have been prepared by specialists in particular branches. Some of these are very good. There is of necessity in such a large book on diet considerable overlapping and repetition. The principal section (Part II) arranges the various diseases, for convenience, in alphabetic order. Each disease is first the subject of a general discussion, after which sample menus are given, followed by general suggestions. Thus, for Addison's disease, it is recommended that the diet be designed to increase gastric acidity and the oral use of dilute "muriatic acid" is advised. The addition of extra protein to the diet is recommended to combat weakness, and it is said, this "will frequently tend to offset this symptom." Foods of a "bland and alkaline character" are to be omitted. A diet "high in sodium chloride" is recommended since "it has been recently proved that a diet high in sodium chloride serves admirably to maintain the body tissue fluid." Olives, pickles, salted crackers and cheese are recommended. It is, of course, dangerous to rely merely on the salt of the food as adequate for sustaining patients with this disease and one should not intimate that such may be the case. The same criticism applies to the recommendations for the treatment of chlorosis. No one relies merely on a diet high in iron content alone for its treatment and this fact should be made clear.

"Commercial fat-free butter" in "minimal quantities," is suggested in the treatment of acidosis. This preparation is unknown to the reviewer. A diet high in calcium is recommended in the treatment of hemophilia. One would expect this to be about as useful as the estrogenic hormone. The diet in angina pectoris is advised to be that used in "uric-acid diathesis" since there is in this malady, according to the author, "a consistent elevation of the blood uric acid." The treatment of diabetes by Short is concise and clear. The chapter on Bright's disease by Mosenthal is excellent. There is a large section on pediatric feeding by N. I. Saxl.

The appendix, bibliography and index occupy the last quarter of the book, 275 pages. A good discussion of alcoholic beverages, with a table of analyses of their food values and composition, together with detailed description of the qualitative ingredients of many mixed alcoholic drinks, from cocktails to *pousse cafes*, is included. The food tables are very comprehensive and appear to be well arranged. They include many commercial preparations in common use, analyses of which have not appeared elsewhere.

G. A. H.

Child Psychiatry. By LEO KANNER, M.D. 527 pages, 17 × 26 cm. Charles C. Thomas, Baltimore. 1935. Price, \$6.00.

In his introduction the author describes the purpose of this book as follows: "The present volume, which is the first textbook of child psychiatry in the English language, is offered as an attempt to cover the entire field of children's personality disorders on a broad, objective, unbiased, and practical basis. It has grown out of everyday contacts with pediatricians, consultation work in a large pediatric clinic and dispensary, collaboration with private practitioners and with the various child-caring agencies of the community, and teaching activities at the Johns Hopkins University School of Medicine. It is intended primarily for physicians and medical students but is also meant to be of help to all those interested in children's behavior problems: social workers, psychologists, sociologists, educators, juvenile court workers, etc."

The book is divided into two parts. The first deals with the principles and methods of psychiatric examination, diagnosis and treatment. In part two the author discusses each clinical entity and complaint which brings a child to a psychiatric clinic, from the point of view of diagnosis, etiology and treatment. Each chapter contains a scholarly historical account of the topic and includes the most important references to the literature. The book, especially the second part, is a useful reference volume. It is liberally supplied with research data from the author's extensive case material. Pediatricians will find it full of practical suggestions for the handling of the behavior and personality problems which they frequently encounter in their practice.

The author has attempted to steer a sane, objective course among the various "schools of thought" which so confuse the student. He has done this so skillfully that the adherents of each school will accuse him of relative neglect of their theories or emphases. The author's leaning is toward the Mevorian school and he gives, in this book, a lucid, readable account of the philosophy and methods of that school, as related to child psychiatry.

H. W. N.

Diabetic Manual for Patients. By HENRY J. JOHN, M.A., M.D., F.A.C.P., Major M.R.C. Second Edition. 232 pages, 13 × 20 cm. C. V. Mosby Co., St. Louis. 1934. Price, \$2.00.

This manual is stated to be "a non-technical guide for the person suffering with diabetes." The author believes infection and overeating are the most important causes of diabetes and that heredity is "really of little importance so far as the individual case is concerned." Diabetes is more common among Jews, he feels, because they are especially prone to overeat and not because of any inherited taint.

This book should be a valuable aid to the intelligent patient. It contains practical suggestions regarding the construction and preparation of diets, the injection of insulin, the treatment of insulin reactions and other questions which frequently present themselves to the patient.

G A H

Brucella Infections in Animals and Man Methods of Laboratory Diagnosis By I FOREST HUDDLESON, Department of Bacteriology and Hygiene, Michigan State College. 125 pages, 24 illustrations. The Commonwealth Fund, Division of Publication, 41 East 57th St, New York City. Price, \$2.25.

This small volume represents a monograph on the laboratory diagnosis of Brucella infections in man and certain susceptible animals. The subject is covered in seven main chapters.

Briefly, chapter one devotes itself to a short natural history of the three forms of this disease, and to the classification, morphology, staining and cultural characteristics of the organisms. Chapter two takes up the methods of isolating Brucella strains of bacteria. Chapter three covers the pathology, of man, cattle and guinea pigs. Chapter four gives the serological methods in common use. Chapter five presents the skin testing or allergic method of diagnosis. Chapter six discusses the opsono-cytophagic power of the blood and its application in diagnosis. Chapter seven discusses the various means at the disposal of laboratory workers for differentiating the three types of Brucellosis. The methods given in these seven short chapters are those which have been found reliable in the author's laboratory. Much of the subject matter represents original work by the author and his coworkers. The remainder represents a selection from the methods of others.

The author has the advantage of a very wide experience with his subject. To his laboratory have come hundreds of strains of the Brucella organism from many parts of the world. His original work in the field has been important. This small monograph is therefore authoritative. It will be of great value to all laboratory workers called upon to assist in the diagnosis of Brucella infections in man or the lower animals.

S L J

is, of course a

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members

The Cyclopedia Corporation of America has presented six volumes of the National Medical Monographs, as follows

- "Diseases of the Chest" by J Arthur Myers (Fellow),
- "The Management of Colitis" by J Arnold Barger (Fellow),
- "Abnormal Arterial Tension" by Edward J Stieglitz (Fellow),
- "Commoner Diseases of the Skin" by S William Becker,
- "Obstetrics for the General Practitioner" by J P Greenhill,
- "Industrial Medicine" by W Irving Clark and Philip Drinker

Eli Lilly and Company have presented to the Library of the American College of Physicians a bound volume entitled "Lilly Research Laboratories Dedication," which are reproduced the addresses and proceedings of the dedicatory exercises held on October 11 and 12, 1934, in connection with the dedication of the new Lilly Research Laboratories

Dr Albert S Hyman (Fellow), New York, N Y, and Dr Aaron E Parsonn (Fellow), Newark, N J, have presented to the College Library their book entitled "The Failing Heart of Middle Life"

Dr Oliver T Osborne (Fellow) New Haven, Conn, has presented to the College Library his new book, "The Evaluation of Symptoms"

Other gifts not previously acknowledged are as follows

- Dr Miles J Breuer (Fellow), Lincoln, Nebr—1 reprint,
- Dr Albert W Bryan (Fellow) Madison, Wis—3 reprints,
- Dr George T Harding (Fellow), Columbus, Ohio—1 reprint,
- Dr Carl R Howson (Fellow), Los Angeles, Calif—1 reprint,
- Dr Archibald L Hoyne (Fellow), Chicago, Ill—4 reprints,
- Dr Henry J John (Fellow), Cleveland, Ohio—1 reprint,
- Dr Henry B Mulholland (Fellow), University, Va—7 reprints,
- Dr Alfred J Scott, Jr (Fellow), Los Angeles Calif—1 reprint,
- Dr Clair L Stealy (Fellow) San Diego, Calif—2 reprints,
- Dr John M Swan (Fellow) Rochester, N Y—5 reprints,

Dr Arthur E Lamb (Associate), Brooklyn, N Y—3 reprints,
Dr Thomas D Masters (Associate), Springfield, Ill—2 reprints,
Dr George W Millett (Associate), Portland, Ore—3 reprints,
Dr W G Weston (Associate), Arkansas City, Kan—2 reprints,
Dr J K Williams Wood (Associate), Willow Grove, Pa—1 reprint

A testimonial dinner was tendered Dr Ernest B Bradley, President-Elect of the College, by the physicians of Fayette County, Kentucky, on June 27, in recognition of Dr Bradley's being elected the President-Elect of the American College of Physicians

Dr Egerton L Crispin (Fellow), Regent and Third Vice-President of the College, received the honorary degree of Doctor of Science on the occasion of the 106th Anniversary of his Alma Mater, Illinois College, at the Commencement Exercises on June 10

Dr Charles L Brown (Fellow) has been appointed professor and head of the Department of Medicine in the Temple University School of Medicine, according to announcements by the University administration recently Dr Brown was at one time instructor in pathology, teaching fellow in medicine, and instructor in medicine in the Harvard University Medical School He became assistant professor of internal medicine in the University of Michigan Medical School in 1928, and was advanced to associate professor of internal medicine in the same institution, beginning July 1929 He became a Fellow of the American College of Physicians in 1929

Dr William Gerry Morgan (Fellow), Secretary General of the College, resigned on July 1 as Dean of the Georgetown University School of Medicine A farewell dinner in his honor was tendered him at the Mayflower Hotel, where sixty members of the Georgetown medical faculty were present to pay tribute to the services of their departing dean

Dr Morgan has retired to private practice, while continuing to serve as a Regent of Georgetown University

Dr Charles R Reynolds (Fellow), Major General, U S Army, has succeeded Dr Robert U Patterson as the Surgeon General of the U S Army

Dr Herbert T Kelly (Fellow), Philadelphia, Pa, was guest speaker on June 21 at the meeting of the Northampton County Medical Society at Easton, Pa, his subject

being "Dependable Laboratory Methods in the Diagnosis and Treatment of Diabetes Mellitus"

The following Fellows of the College were guest speakers on the program of the Tennessee Valley Medical Association and Post-Graduate Assembly at Knoxville, Tenn, June 26 to 27

Dr W D Stroud, Philadelphia, Pa—"Coronary Disease, Including Angina Pectoris",

Dr James E Paullin, Atlanta, Ga—"Arthritis",

Dr Lyle Motley, Memphis, Tenn—"Clinical Value of the Electrocardiogram in Diseases of the Heart"

Dr Ralph H Kuhns, Chicago, Ill, Instructor in Neuropsychiatry at the University of Illinois College of Medicine, will address the annual convention of the American Congress of Physical Therapy in Kansas City, September 9, on "Fever Therapy in Dementia Paralytica"

Dr James W Hunter, Jr (Fellow), Norfolk, Va, became President of the Norfolk County Medical Society during June of this year Dr Walter B Martin (Fellow), Norfolk, Va, was made President-Elect at the same time

The Mississippi Valley Medical Society has been organized to conduct the Tri-State Post-Graduate Assembly of Illinois, Missouri and Iowa The first annual meeting will be held in Quincy, Ill, on October 2, 3 and 4, 1935 Dr Harold Swanberg (Fellow), Quincy, has been elected Secretary-Treasurer Among Fellows who will address the first assembly are

Dr Albert Sorland, Los Angeles, Calif,

Dr William C MacCarty, Rochester, Minn

Dr Albert S Hyman (Fellow) will give two lectures upon resuscitation of the dying heart at the VII International Medical Post-Graduate Congress of the University of Brussels which meets at Spa, September 20 to October 2, 1935 Dr Hyman will also speak before the Royal Academy of Medicine in Rome on October 5, and at the University of Bologna on October 7

Dr William B Dewar (Fellow) and Dr Hubert B Haywood (Fellow), of Raleigh, N C have been appointed Professors of Medicine in the Wake Forest College School of Medicine

Dr Charles J Bloom (Fellow), of New Orleans, has been elected President of the Louisiana Pediatric Society

Dr Louis H Behrens (Fellow), of St Louis, delivered the valedictory address to the graduates of the St Louis College of Pharmacy on June 6 Dr Behrens had graduated from this institution in 1888

LOCAL MEETING OF THE FELLOWS AND ASSOCIATES

OF THE

AMERICAN COLLEGE OF PHYSICIANS IN THE DISTRICT OF COLUMBIA

On April 16, 1935, a group of the civilian Fellows and Associates residing in the District of Columbia met at the Gallinger Municipal Hospital for a clinical session followed by luncheon Dr Thomas S Lee, Professor of Cardiology at Georgetown University School of Medicine, gave a talk and clinical demonstration on the subject of auricular fibrillation Dr Walter A Bloedorn, Professor of Medicine at George Washington University School of Medicine, gave a talk on the various types of obesity and their treatment Dr Charles P Cake, Instructor in Clinical Medicine at Georgetown University School of Medicine, discussed the surgical treatment of pulmonary tuberculosis Dr Walter Freeman, Professor of Neurology at George Washington University School of Medicine, demonstrated on a patient with traumatic transection of the spinal cord the various technical procedures in diagnosis, including combined cisternal and spinal punctures The session was presided over by Dr Wallace M Yater, Professor of Medicine at Georgetown University School of Medicine and Governor for the District of Columbia of the American College of Physicians Dr Wm Gerry Morgan, Dean of the Georgetown University School of Medicine and Secretary-General of the American College of Physicians, addressed the group, reporting upon the various activities and the history of the College Luncheon was tendered by Dr Edgar A Bocock, Superintendent of the hospital This is the first of such meetings to be held in the District of Columbia It is hoped that next year several adjoining states will arrange such a program together

OBITUARIES

GEORGE E BETHEL

Dr George E Bethel, Dean of the School of Medicine of the University of Texas, died April 17, 1935, from cardiac and renal complications of essential hypertension after an illness of about five months

Although but 40 years of age, Dr Bethel had rendered a signal service to the University of Texas in the field of medical education After his graduation in medicine from the University of Texas in 1923 he became, successively, Adjunct Professor and Associate Professor in the Department of Anatomy in his alma mater, a service which extended over two years During 1925 he was an intern in Philadelphia General Hospital, and in 1926 was advanced to the position of assistant chief resident physician of that institution In 1927 and 1928 he was in charge of the Health Service of the University of Texas at the Main Branch of the University in Austin, from which position he was called to fill the deanship of the School of Medicine in Galveston in 1928 The latter office he held continuously up to the date of his death

During his student years he won membership in the Alpha Omega Alpha honorary fraternity He was a Fellow of the American Medical Association, and was elected to Fellowship in the American College of Physicians April 7, 1929

Dr Bethel's comparatively short term of office as Dean of the School of Medicine of the University of Texas, combined with the fact that he had not been in robust health for several years, prevented his attendance upon many gatherings of medical educators Despite these handicaps, however, the excellence of his service in the deanship cannot be overstated His one interest in life was the advancement of the Medical School, and the proper functioning and integration of its various units received his constant and thoughtful consideration It is said that he knew personally and intimately every student in the School of Medicine He knew those who were fitted for advanced study and research, as well as those who needed guidance, those who required assistance, and even those deserving punitive measures because of lagging scholarship or for other reasons His constant and unflinching devotion to the welfare of the School of Medicine, its teaching staff and student body, was appreciated by all who knew him He was widely known throughout the state, not only by the medical profession but among the laity and other professional and educational groups as well So highly was he esteemed by the members of the Texas Legislature that the Senate of the state, which was in session at the time of his death, memorialized his passing with appropriate resolutions

Dr Bethel was a man of high moral principles, of abiding devotion to his duty and of unflinching fairness to all with whom he came in contact His

capacity for inspiring students who came under his supervision with the loftiest ideals and the highest ethical principles will long be remembered

CHARLES T. STONE, M.D., F.A.C.P.,
Governor for Texas

JOHN WILLIAM WARNICK

Dr. John William Warnick (Associate), Johnsonburg, Pennsylvania, died April 12, 1935, of diabetes mellitus and complications following an illness of more than a year. Dr. Warnick was born in 1863, and graduated from the University of Pittsburgh School of Medicine in 1896. He was a member of his county and state medical societies, and a Fellow of the American Medical Association. He was at one time county medical director, and for more than twenty years he was a member of the Board of Health in Johnsonburg. He was also President of the U. S. Board of Pension Examiners. He became an Associate of the American College of Physicians in 1925.

ANNALS OF INTERNAL MEDICINE

VOLUME 9

SEPTEMBER, 1935

NUMBER 3

PULMONARY FIBROSIS AND EMPHYSEMA *

By JAMES ALLAN DER MILLER, A M , M D , F A C P ,
New York, N Y

IN the consideration of these chronic pulmonary conditions I propose in the first place to present them not as independent clinical entities but as coexistent conditions mutually dependent upon each other and associated with all chronic lung disease of whatever causation, and secondly, to emphasize the clinical importance of the functional pathological changes associated with these conditions, as distinct from the tissue pathological changes with which their names are usually connected

DEFINITIONS

We might begin this consideration with our definition of these conditions in terms of function

Pulmonary fibrosis we would define as an irreversible failure of the self-cleansing power of the lungs

Emphysema we would define as the irreversible failure of the pulmonary retraction power

In order to make our meaning clear we may explain that in the case of fibrosis any form of air space obliteration in the lungs (atelectasis, edema, infiltration) is essentially a phenomenon involving both failure of the respiratory and of the self-cleansing functions. Usually the condition is reversible, and then the affected lung areas may reestablish their function. If, however, the failure becomes permanent, then pulmonary fibrosis is the result, as an expression of the irreversible failure of the self-cleansing power.

In the case of emphysema we have a hyperdistention of certain lung areas, with unequal distribution of the air in the lungs. This condition is at first reversible, as in what we are accustomed to call compensatory emphysema, that is, if the causative factor is removed, the normal retraction power of the affected areas may reassert itself. If, however, the untoward conditions are prolonged, or, as in old age, essential pulmonary tissue changes have occurred, then the retraction power of the lungs cannot be regained,

* Read at the Philadelphia Meeting of the American College of Physicians, April 30, 1935

From the Tuberculosis Service of Bellevue Hospital, New York, N Y

that is, the condition becomes irreversible and true emphysema results. How these two conditions, fibrosis and emphysema, interact upon each other, and how the distribution of each in the lungs is affected by the other, will be emphasized and their clinical significance discussed.

The ideas expressed in this paper are due largely to the stimulus gained from the interest in the functional pathology of the lungs which has been developed by Dr Israel Rappaport of our staff, and we have also been fortunate in obtaining the cooperation of Dr Dickinson Richards of the Presbyterian Hospital and Dr André Couinand of our Bellevue staff in the elaboration of the technical details. I am under great obligation to these associates for aid in the preparation of the material here presented.

THE FUNCTIONAL PATHOGENESIS OF PULMONARY FIBROSIS

The lungs present the most extensive surface of the body that is exposed to the outside air. On account of this exposure as well as the delicacy of their structure, the lungs need special protection to preserve their most important vital function, namely, respiration.

Damaging influences from the outside air are of various sorts. They may be infectious, chemical, or physical in nature, but the damage produced results in each instance in the same tissue response, namely, the replacement of specifically organized tissue by nonspecific connective tissue.

The effects of these influences are frequently most marked in the lower and posterior areas of the lungs, as these regions are more directly exposed through the larger descending bronchi and also because they are the most dependent portions and so less amenable to natural drainage. We consequently are apt to find many forms of pulmonary fibrosis most regularly in the lower lobes.

The pathogenesis of this condition may be considered first as bronchial infection or exudation, with the action of the ciliated epithelium impaired or destroyed, the normal bronchial movements impeded and the air passages occluded. Then follows the clogging of lymphatics through an exudate of large mononuclear cells commonly designated as "dust cells", and this exudate later becomes organized into fibrous tissue, which begins to form in the walls of the bronchi and gradually extends into the peribronchial tissue, resulting in diminution of efficient respiratory space, impairment of self-cleansing function, and increased susceptibility to subsequent bacterial infections.

CLINICAL FORMS OF FIBROSIS

There are certain characteristics common to all forms of pulmonary fibrosis of whatever etiology, but for convenience the conditions may be divided into certain clinical categories.

1 *Pre-Clinical Forms* Under ordinary conditions of modern life, particularly in cities, the lungs of all persons are constantly exposed to

various of the damaging influences already mentioned. Everyone is exposed to frequent repetitions of minor pulmonary infections such as common colds, grippe, bronchitis, etc. In cities and industrial centers the lungs are exposed to constant aspiration of particulate matter, fumes and gases. The cumulative effect of these influences invariably results in a certain degree of pulmonary fibrosis. Some individuals are more predisposed than others because of the nature of their environment, or perhaps particularly because of certain constitutional characteristics, and as age increases, the cumulative effect of these influences of course becomes more pronounced. In the majority of instances the total effect is comparatively slight, the ability of the lungs to continue normal function is great, and the fibrosis that occurs does not present a clinical problem. But nevertheless it must be borne in mind as a basis upon which under more severe or more prolonged injurious influences definite damage occurs, with definite clinical symptoms.

2 Infectious Fibroses These forms of pulmonary fibrosis are those which have involved the parenchyma of the lungs in the manner already described, as the result of more or less well defined clinico-pathologic lung conditions of an infectious nature. Here are included all of the usual chronic lung infections such as pulmonary tuberculosis, interstitial pneumonitis, chronic suppurative conditions, and the like.

3 Occupational Fibroses These are usually included under the general term of pneumokoniosis,—of which silicosis is the best known example. They are fibrotic processes involving primarily the lymphatics of the lungs which represent the results of considerable or prolonged exposure to industrial dust or other similar agents.

4 Vascular Fibroses This type is really a pulmonary arteriosclerosis and includes the fibrotic processes affecting primarily some part of the vascular system of the lungs. Many of these forms are of unknown etiology, but some of them are well recognized clinical entities, particularly those in which the pulmonary changes are associated with chronic valvular heart disease or with chronic cardiovascular disease, and likewise that interesting clinical condition which we have come to know under the name of Ayerza's disease.

It must be understood that the line of cleavage between the processes included in these four groups is never very sharp. The pre-clinical fibroses gradually go over into the infectious or industrial forms, the infectious forms include many conditions which border on the industrial types, and again in the pneumokonioses, supervening bronchiectatic or pleuritic processes may add a purely clinical element to the picture, and, finally, more or less vascular sclerosis is characteristic of all other forms of pulmonary fibrosis, although it is only in one distinct group of conditions that this appears to be the chief pathological basis of the disease.

THE FUNCTIONAL PATHOGENESIS OF PULMONARY EMPHYSEMA

The cause of pulmonary emphysema has been the subject of extensive controversy which is not yet satisfactorily settled. It may therefore be helpful to review briefly some of the various theories which have been advanced to explain the pathogenesis of emphysema, as a basis from which we may lead up to more modern concepts.

It is well known that emphysema develops in old people. It is an invariable accompaniment of the aging process and in this sense may be considered as a physiological change. When however, as is not uncommon, this condition develops in a person under 50 years of age, it may be considered pathological.

The production of pulmonary emphysema has long been ascribed to individual constitutional characteristics, and it has been suggested that these may be hereditary. It has been noted also that such tendencies are accentuated when the work of the individual entails exertion out of proportion to his constitutional capacity.

Again, it has been observed that emphysema may be brought about by prolonged intrapulmonary pressure due to air passage obstruction, as in bronchial asthma or in more chronic obstructing conditions.

Its causation has also been ascribed by Freund¹ to immobilization of the bony thorax associated with calcification of the rib cartilages or of the intervertebral disks, and this view has in the past been widely accepted. It is challenged, however, by Schenker² who believes that the chest wall changes are primarily a chronic contraction of the intercostal muscles, leading to fixation of the chest in the expanded position, and that the bony changes are secondary to this. In a similar way, flattening and immobilization of the diaphragm widen the costal arch and lead to fixation of the lung, and this has been looked upon as an accessory cause of emphysema.

Also the fact that the upper accessory muscles of respiration are brought prominently into play and become chronically contracted, has been thought to be an explanation of the tendency of emphysema to localize itself in the upper and anterior portions of the lungs.

The association of emphysema with cases evidencing failure of pulmonary circulation, as in chronic cardiac and cardiovascular disease, has long been recognized and explained on the basis of the increased fixation of the chest cage.

The picture is further complicated by the clinical recognition of what we term compensatory emphysema. When a considerable portion of the lung loses its normal ventilatory function from any cause, then the remaining lung areas take on added activity and the alveoli dilate to compensate for this loss. This condition is frequently confused with true emphysema, but as van Leeuwen and his associates³ have shown in their studies of asthma and emphysema, compensatory emphysema is a reversible and consequently recoverable condition. Often a return to normal occurs when

the bronchial obstruction or other cause of ventilatory embarrassment is relieved. Emphysema which is at first compensatory and reversible may become permanent and irreversible, but only after a protracted time and comparatively rarely.

There is still another condition, not so generally recognized, although it was originally described by Laennec⁴ and has recently again been emphasized by another French clinician, Cécile,⁵ namely, pulmonary hypertrophy. This is a true regeneration of new lung tissue as a compensatory process, and is neither the temporary passive distention of existing lung areas, compensatory emphysema, nor the permanent loss of lung retraction power, true emphysema. We shall return to the consideration of this most interesting lung condition later in our discussion of intrinsic lung function.

Modern Concepts It remained for Neergaard⁶ to furnish the most modern and most brilliant conception of the pathogenesis of emphysema.

He considers the condition, as we do, as an irreversible loss of retraction power in the lung. This retraction power has always been considered, however, the function of the recoil of the elastic tissue of the lungs.

Neergaard recognizes this function, but considers that it represents only 25 per cent of lung retraction power. The dominating 75 per cent of this power he believes is exerted by the surface tension which develops at the point of contact between the air and the film of moisture which covers the alveolar walls and the capillary air passages. This tension acts in the same direction and in association with the recoil of elastic tissue.

When interruption of communication occurs in a large number of air passages, as, for example, from exudates or bronchial muscle spasm, a compensatory hyperexpansion occurs to open up these communications, and the pulmonary elasticity is increasingly called upon. This overexpansion of alveolar surface of necessity diminishes the surface tension, and the retraction power suffers. As the hyperexpansion continues, the return to the normal becomes increasingly difficult, although the elastic forces of the chest wall are now favoring expiration instead of inspiration, and at best the lung can return from a condition of *volumen pulmonum auctum* to a position of normal inspiration, and this is the state of irreversible emphysema.

Luisada,⁷ who has also made valuable contributions to the modern knowledge of emphysema, believes that inflammatory changes in the air spaces lead to degeneration of the smooth muscle tissue in the walls of the bronchioles and alveolar ducts, and he considers that these changes, in conjunction with the factor of diminished surface tension noted by Neergaard, favor the development of the distended air spaces, the thinning or breaking-through of the alveolar walls, and the loss of elasticity and retraction power of the lungs, all of which are characteristic of irreversible emphysema.

Therefore, according to these observers as well as other modern students of the subject, the original cause of emphysema arises in the air spaces and is usually in the nature of an inflammation. The associated changes

in the chest wall, which have been above described as the cause of emphysema, would consequently, according to this hypothesis, be secondary processes resulting from the effort to compensate for the failure of the retraction function of the lung

So, finally, we find that in emphysema, as in the case of pulmonary fibrosis, we must look for the first evidences in the air spaces themselves. This, as we shall see later in our consideration of the clinical features of these diseases, attaches a very important significance to those early and slight manifestations of pulmonary dysfunction which are often looked upon as cases of simple bronchitis of no serious significance.

Viewed from this angle, the close association which has always been recognized to exist between fibrosis and emphysema and bronchitis, does not necessitate an explanation of the bronchitis as secondary to the fibrosis and emphysema, but rather the so-called bronchitis, when prolonged or often repeated, would be the early manifestation of the more serious failure of lung function which we recognize clinically as fibrosis or emphysema.

THE RECIPROCAL RELATIONSHIP BETWEEN PULMONARY FIBROSIS AND EMPHYSEMA

This similarity in their method of pathogenesis is only the beginning of the close connection which exists between these two conditions. They are almost always associated together, when one is found the other also exists, but in another portion of the lung, and they are mutually dependent upon each other.

We have already noted that fibrosis is often found in the lower and posterior portions of the lungs and that emphysema is found predominantly in the upper and anterior portions.

If the fibrosis is a localized one in the upper lobes, due to infections such as tuberculosis or other chronic diseases, then emphysema is also found, first in the neighboring lung areas, but also in distant points if the fibrotic process is extensive enough. The same condition of affairs is found in pneumokoniosis and in vascular fibrosis, both of which are invariably associated with emphysema.

Such emphysema secondary to fibrosis may be of the compensatory type and reversible. But if long continued, the condition becomes irreversible and true permanent emphysema results as the retraction power of the lung fails.

On the other hand, if the emphysema is the primary and predominant condition, situated, as we have seen, mainly in the anterior upper lobes, then the hyperexpanded lung exerts pressure upon the other lung areas and bronchial drainage function in them is impaired and fibrosis results. These changes are most regularly found in the posterior and lower lobes.

So, we thus find these two conditions going hand in hand as the accompaniments of all chronic lung disease, and we can therefore think of them

no longer as two absolutely distinct diseases but rather as one combined clinical entity which we may term, in general, chronic lung disease

THE CLINICAL PICTURE OF CHRONIC LUNG DISEASE

In the early stages of these conditions there may be no symptoms or other clinical manifestations even though the underlying basic changes may already be quite definite and considerable, as was pointed out in our consideration of the pre-clinical forms of pulmonary fibrosis. When the changes are sufficiently advanced both in tissue and functional pathology, then certain symptoms present themselves.

Symptoms These symptoms are most regularly cough, expectoration and dyspnea. When the disease has become so advanced as to seriously impair cardio-respiratory function, then cyanosis also appears, and when the basic conditions of fibrosis and emphysema are associated with or dependent upon bacterial infection, then we usually have also fever with its accompanying systemic symptoms.

Of all these various symptoms the characteristically important one from the standpoint of function is *dyspnea*, and it is this symptom which most regularly and constantly brings these conditions to our attention clinically.

The recent studies of dyspnea, which Drs. Cournand, Brock, Rappaport and Richards⁸ have been making, are of considerable interest, as they appear to demonstrate that dyspnea in these cases of fibrosis and emphysema is not due to chemical changes in the blood but rather to the failing coordination in the neuromuscular apparatus of respiration. This new concept of dyspnea as a subjective sensation referred to the breathing apparatus places the responsibility for its causation upon failure of lung function, and may be most helpful in furthering our knowledge of functional pathology of chronic lung disease.

Physical Signs From the standpoint of examination, while the physical signs may be varied and frequently quite marked, it is well known that they are very often not characteristic and that the associated presence of fibrosis and emphysema in the lungs tends to modify and obscure such physical signs as may be characteristic if either condition be present alone. We therefore find that physical examination is of comparatively subordinate importance.

Roentgenological Signs The most fruitful source of information is the roentgenogram. But here also we encounter practical difficulties similar to those described with physical examination, and for the same reason, namely, the tendency of associated emphysema and fibrosis to mutually obscure each other. Roentgenologists have noted the fact that with the ordinary routine technic it has often been difficult to obtain a correct pathological interpretation of the roentgenogram of these combined conditions, but the true significance of this fact is often not recognized. Even profound students of roentgenology do not as yet thoroughly understand the physical and optical laws which underlie this reaction, the effects of

which however are obvious. For example, the liver, normally densely opaque to the roentgen-ray, may become translucent when a large loop of bowel distended with gas overlies it, or the filtration effect of the bony rib makes obvious a density in the underlying lung, which same density is invisible in the intercostal spaces by the same ray, or again extensive fibrotic processes in lung or pleura obscure underlying cavities in the ordinary roentgenogram, which can easily be brought out by special procedures and different penetration. This being so, it is easily understandable how fibrosis, which produces increased densities, and emphysema, which is associated with increased air content, would not only very definitely affect the roentgenological picture in themselves but also have mutually important influences upon each other. Therefore it is of great practical importance to appreciate the limitations of the roentgenological method of examination in the interpretation of pulmonary lights and shadows in terms of definite pathological conditions, unless special technical precautions are taken to avoid error.

Such thorough students of the subject as Pancoast and Pendergrass⁹ in silicosis and Fray¹⁰ in emphysema, have done much to increase our roentgenological knowledge of these conditions. But they too have recognized the limitations and possibilities of error in roentgenography. In the cases of silicosis, Bentker,¹¹ who has recently studied this subject thoroughly both from the roentgenological and functional standpoint, has definitely come to the conclusion that the evaluation of the functional disturbances, particularly as evinced by dyspnea, is the more important and valuable method of study.

Functional Tests We therefore find a demand gradually asserting itself for some clinically applicable measure of pulmonary functional impairment. Such a measure of function should aid not only in detecting the presence but also in estimating the severity of such conditions as fibrosis and emphysema of the lung. It should be of assistance not only in determining the extent of the lesions but particularly in assessing the degree to which each patient has achieved a functional adaptation to his pulmonary damage.

Slow progress is being made in attempts to devise laboratory or clinical functional tests which will be of assistance to our understanding of these and similar diseases. Up to the present time it must be admitted that the value of these tests is somewhat limited and that the conclusions to be drawn from them must still be considered to be of a tentative nature. It may be of interest, however, to review a few of the tests which are being employed by workers in this field.

It would appear that such functional studies might be of the greatest importance in the question of prognosis for extraordinary variations in tolerance to apparently similarly extensive disease are found. Also they may afford an opportunity to discover constitutionally predisposed individuals and to remove them from untoward conditions of work or other environment before advanced and debilitating disease has resulted. Finally, in the now rapidly growing field of thoracic surgery for various chronic

diseases these tests may afford a basis for better selection of suitable operative risks and point the way to appropriate measures to meet emergencies which may arise during or after such operations

Some of the more usual functional tests are as follows

FUNCTIONAL TESTS OF THE LUNGS

I The study of the statics and dynamics of the breathing apparatus

A The determination of lung volumes

The purposes of this study are

- 1 To measure the volumes of air available for normal breathing (tidal air) and for extreme breathing (vital capacity and its two components, complementary air and reserve air)
- 2 To measure the volume of air which is constantly present in the lungs and in which the mixing of the gases takes place (residual air)

The graphic method is the best for recording the vital capacity

The determination of the residual air is based upon the method of mixing of a known gas, derived from the work of Van Slyke and Binger. For clinical purposes Christie has described a method whereby oxygen is used as a mixing gas. Hurtado et al. have published statistical studies in normal, emphysematous and fibrotic cases. They emphasize the relationship between the different components of lung volumes on the one side and the total capacity on the other, and they furnish numerous data as to the variation in the different ratios in pathological cases. The graphic registration of lung volumes, either alone or in connection with a parallel study and recording of pleural pressure, as proposed by Koontz and Meakins and Christie, provides valuable information concerning the elastic state of the lungs.

Although the employment of this method of study of lung volumes is widespread, the warning is justified that conclusions from such studies should be submitted to rigid criticism. First, because the method of estimation of the residual air is based on the assumption that mixing in the lungs is quite homogeneous, which in cases of emphysema is far from true. Richards, Cournand and Larsen have recently undertaken studies to determine the limits of error in this method and the possible corrections to be used. And, secondly, because the study of the vital capacity

measures the maximum volume available for breathing purposes without any reference to the power of endurance, in other words without taking into account the efficiency of the functioning breathing apparatus

B Spirometry

This method has a great advantage in fulfilling the above requirement, namely, the measurement of the efficiency of the functioning breathing apparatus. It is simple, physiological, and based upon the recording of the breathing upon slow and rapid moving drums, with reference to time. The rate and depth of the breathing may be easily studied on the graphs, as well as the form of each breath, the slope of the curve, especially the end of each phase, the pause, the variation of the level of the resting position. Indirectly also this method permits estimation of the speed of the airflow, which is related to the state of the air passages and the dynamics of the breathing apparatus (diaphragm and moving chest cage). The use of adrenaline injection, by modifying the state of bronchial resistance permits a better analysis of the phenomena.

Maximum voluntary breathing in a standard time should also be recorded and studied on the basis of the volume of each breath and the volume of air breathed per second, and compared with the vital capacity tracings.

It is to be hoped that the pneumotachographic method invented and developed by Fleisch may become available for clinical purposes, as it registers directly the change in the speed of the airflow and at the same time the form of the breathing.

II The study of the lesser circulation

A Venous pressure

The best physiological method available is the direct method of Moritz and Tabora. The position of the right auricle which determines the zero point for the measure of venous pressure being quite variable according to the distention of the thoracic cavity in emphysema, lateral roentgen-rays of the chest should be taken. The variation of the venous pressure should be recorded in connection with the phase of respiration and its variation of amplitude, thus affording information concerning the dynamics of the venous return to the chest.

As an index of the ease with which the blood passes through the large veins, right heart and pulmonary vascular bed, an elevated venous pressure indicates increase of resistance somewhere in the vascular path. Despite reports in the

literature to the contrary, in moderate and advanced emphysema the venous pressure is often normal or even abnormally low

A recent test associated with the measurement of venous pressure has been devised by Caughey to estimate the capacity of the heart and of the pulmonary vascular bed to take care of an added load of fluid infused in a standard time. This test has a practical value for determining the individual case in which saline infusion or blood transfusion may be indicated or contraindicated, particularly after surgical operations

B Blood velocity

This is a measure of the linear velocity of the column of blood through a known segment of the circulatory system, including the whole lesser circulation. The path goes from the antebachial vein through the right heart and the vascular bed of the lungs ending in different parts of the arterial system, according to the method employed. The cyanide method, whereby the gasping reflex is set up when the head of the column of blood carrying the cyanide reaches the sinus carotides, seems to give the most definite end-point

As the various parts of this system are subjected to variable influences whenever pathological conditions are present in the lungs, efforts have been made to isolate smaller portions, for instance from the antebachial vein to the alveolar area, by using intravenous injections of ether. The reliability of this method is still doubtful

In fibrosis and emphysema the blood velocity throughout the whole system is usually above the upper limits of normal

C Cardiac output

The measure of the cardiac output or minute volume of blood passing through the lungs is based on methods involving either the Fick principle whereby mixed venous blood CO_2 is equilibrated with a known mixture of CO_2 , or ventilation of foreign gases (Grollmann)

As far as we are aware, the poor and uneven diffusion of gases through the lungs in cases of emphysema, limits the applicability of these methods

III The study of the physico-chemical state of the arterial blood

A Arterial puncture

This is definitely a clinical method of investigation and affords unique information as to the O_2 saturation, CO_2 content and pressure, level of the CO_2 dissociation curve, pH, etc., but it requires accurate analysis by the Van Slyke-Neill manometric apparatus. It brings out the integration of the three

main factors, namely, ventilation, diffusion of the gases, and perfusion of the lungs

Clinically it gives indications as to the advisability of O_2 therapy and enables one to follow its action

B Alveolar samples

The analysis of alveolar samples of air is not a substitute for the previous method, particularly in emphysema and fibrosis. The uneven specimens obtained in these conditions, the poor approximation of the arterial CO_2 per cent and the alveolar CO_2 per cent, are good proof of the variability of the ventilatory condition prevailing throughout the lungs in these diseases

IV The study of the total ventilation

The measure of the total ventilation with the Tissot apparatus and the estimation of the O_2 intake and the CO_2 output determines the metabolic rate of the body and the level of ventilation required

V Exercise tests

In recent years the value of the duplication of most of the above tests during exercise has been emphasized. In the hands of various workers the type of exercise varies, from stepping up and down stairs, to a fixed task performed on a bicycle, with the recording of the work done in terms of kilowatts. Whatever method is used, it seems that the form of exercise should produce conditions under which the patient is able to feel the strain, and it should be most flexible. It is under conditions of actually increased tissue demands that the efficiency of the breathing apparatus should be tested.

Special attention should be given to the form, amplitude, rate of breathing, total ventilation per period of time, O_2 intake, arterial saturation, and finally to the level of the CO_2 dissociation curve. These data should be observed during the recovery as well as during the exercise period.

In general, it should be emphasized that none of the functional tests should be interpreted separately, neither should they exclude other clinical data, particularly linear chest measurements, and observation and recording of the chest and abdominal walls, either by simple inspection or with the help of the fluoroscope or roentgenogram.

Among the very numerous functional tests which have been suggested, the above have been chosen as the most practical and they are the ones that are being used routinely in the functional study of chronic pulmonary disease in our Service in Bellevue Hospital.

These and other methods are the type of studies which are beginning to be developed and which will certainly play an increasingly important part in the clinical study of various lung diseases.

CLINICAL CLASSIFICATION

For practical purposes the clinical evolution of chronic pulmonary disease may be separated into three phases

1 *The Bronchial Phase* It has already been brought out in our discussion of the pathogenesis of fibrosis and emphysema that the primary cause has been found to lie in the air passages, so that in the earlier phases, while the process is mild and well compensated, it remains localized in these passages. There may be temporary or localized pulmonary congestion with interference of drainage function, which manifests itself by a group of symptoms usually attributed to bronchitis. We also see these changes going over into chronic persistent bronchial catarrh, frequently associated with allergic asthmatic paroxysms in predisposed individuals. This predominantly bronchial phase may persist for a long time before a definite or marked change in lung function occurs.

The recognition of the importance of this bronchial phase as the forerunner of serious lung disease has already been emphasized, and from a clinical point of view it would appear that this is the phase in which properly directed protective measures might control the development of serious disease. Effective preventive treatment of cases at this stage in time might considerably diminish the prevalence of the more serious lung conditions, fibrosis and emphysema.

2 *Pulmonary Phase* Sooner or later if the bronchial condition persists, general lung function shows increasing signs of embarrassment which requires definite compensatory effort, and then the clinical picture takes on the aspect of real pulmonary disease. In the literature we find this phase described either as chronic emphysema and bronchitis, or as chronic pulmonary fibrosis associated with bronchitis or bronchiectasis, or as a combination of these conditions, with or without specific associated infection as in tuberculosis. For, as is very evident, the transitions and interactions of these conditions from one to another are very fluent.

3 *Respiro-Circulatory Decompensation Phase* As the conditions persist and advance, increasing respiro-circulatory embarrassment is evident, and then cardio-circulatory compensatory effort becomes a conspicuous feature of the clinical picture. Hence, we may call this phase the respiro-circulatory decompensation phase. It is extremely important to recognize the interdependence of the respiratory and circulatory function in advanced pulmonary disease. Yet in the later stages the interaction is so confused that it is frequently difficult to state whether the symptoms presented are due mainly to respiratory or, on the other hand, to circulatory decompensation. This interacting relationship between cardiac and respiratory function in chronic lung disease has been very brilliantly brought out by Castex and Capdehourat¹² in their study of that most interesting condition known as Ayeza's disease. While it is often extremely difficult to assess the relative importance of the respiratory and circulatory function, from the

clinical point of view the important thing to emphasize is then close interaction, and to realize that in the end-stages of chronic pulmonary disease failure of function in both of these vital systems may develop

INTRINSIC LUNG FUNCTION

Having presented pulmonary fibrosis and emphysema as the fundamental bases of all chronic lung disease, and having attempted to interpret these conditions as essentially disturbances of function, I wish, in conclusion, to suggest the consideration of a hypothesis which may aid our further thinking along these lines

For several years Dr. Rappaport of our staff has clung to the conception that there must reside in the lung a power of prompt adaptation to the changing demands upon respiration, which power cannot be adequately explained by the prevailing concepts of the lung as a simple mechanically elastic organ. Evidence is apparently accumulating in favor of some such conception, which we may designate tentatively as intrinsic lung function.

In our discussion of compensatory emphysema we called attention to the fact that over a century ago Laennec recognized pulmonary hypertrophy as distinct from emphysema, and that Celice has recently repeated these observations.

More recently still, Hilber¹³ has offered some very convincing experimental evidence in rats, demonstrating that following the extirpation of one lobe of the lung, the remaining lung areas compensate for the loss not only by ballooning-up, that is, by compensatory emphysema, but also by genuine regeneration with new formation of perfectly efficient lung tissue with corresponding new bronchi, new vessels and new respiratory alveoli.

The increasing vogue of lobectomy in the surgical treatment of various lung conditions should in the near future offer important histological evidence concerning the occurrence of such regeneration of lung tissue in human beings, and clinically there is already some evidence in its favor from the fact that following lobectomy the remaining portion of the lung comes to replace most of the space formerly occupied by the excised lobe, without however the occurrence of the usual evidences of emphysema. As far as I am aware, however, no histological evidence is as yet available in cases where these conditions have existed a sufficiently long time, to determine whether or not true lung regeneration has occurred.

Hilber believes this regeneration to be dependent in some way upon changes of air currents produced by the extirpation of the lobe.

This evidence is new and important but still such regeneration takes some time, and readjustments of function would appear frequently to take place more promptly than can be entirely explained by this regenerative process. In this connection Orsos¹⁴ has however, also very recently, in his studies of the respiratory epithelium, reported upon histological evidence of a remarkable continuous change which goes on over the breathing surface of the lung.

We offer the hypothesis that perhaps these experiments as well as clinical evidence suggest the possibility that the breathing surface represents an extraordinary surface structure of the body, which can adapt itself to its unique task by so rapid and constant a change of its elements as to enable it to retain its extreme delicacy in spite of its vast exposure to damaging influences, and at the same time to retain its adaptability to the great strain of constant respiratory and circulatory movements

If some such theory could be sustained, it would be of outstanding importance in the solution of many vexing problems

We do not, however, need to resort to the hypothetical in order to emphasize the importance of functional pathology in the study of lung diseases

The field is difficult but extremely fascinating, and we have as yet advanced only to the threshold of our knowledge of it. Continued scientific and clinical research will make for progress which it will well repay us as clinicians to follow with keen interest and appreciation if we are properly to understand many of the intricate problems of chronic lung disease

BIBLIOGRAPHY

- 1 FRUEND, W A. Über primäre Thoraxanomalien, speziell über die starr Dilatation des Thorax als Ursache eines Lungenemphysems, 1906, S. Karger, Berlin
- 2 SCHENKFF, D. Beziehung zwischen starrer Thoraxdilatation und alveolarem Lungenemphysem, Dissertation, 1910, Brin and Co., Basel
- 3 VAN LEEUWEN, W St., VAN NIEFKERK, J., and WILTZ, G A. Studien über Atmung und Thoraxform bei Asthma und Emphysem, München med. Wchnschr., 1933, lxxx, 681
- 4 LAENNEC, R TH H. Traite de l'auscultation mediate, 1819, J A. Brosson and J S. Chaude, Paris
- 5 CILICE, J. L'hypertrophie du poumon, Paris med., 1929, i, 353-356
- 6 NFERGAARD, K. Beitrag zur Lehre vom Emphysem, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1930, xlii, 624
- 7 LUISADA, A. Über Lungendynamik, Ergebn. d. inn. Med. u. Kinderh., 1934, xlvii, 92-184
- 8 COURNAND, A., BROCK, H J., RAPPAPORT, I., and RICHARDS, D W. Disturbed action of respiratory muscles as a contributory cause of dyspnea. (To be published in the Arch. Int. Med.)
- 9 PANCOAST, H K., and PENDERGRASS, E P. Roentgen technic with especial reference to examination to diagnose or exclude silicosis, Jr. Indust. Hyg., 1934, xvi, 165-168
- 10 FRAY, W H. Roentgenologic diagnosis of chronic pulmonary emphysema, Am. Jr. Roentgenol., 1934, xxxii, 11-22
- 11 BEINTKER, H. Die schwere Staublunge in der Versicherungsgesetzgebung, Schriften d. Gesamtgebiet d. Gewerbehygiene, Heft 43, 1933
- 12 CASTEL, M R., and CAPDEHOURAT, E L. Chronologie et phenomenologie des alterations morbides chez les "cardiaques noirs" de Ayerza, Presse med., 1934, xlii, 268-272
- 13 HILBER, H. Experimentell erzeugte Lungenregeneration, Verhandl. d. anat. Gesellsch., 1934, xlii, 189
- 14 ORSOS, F. Das Epithel der Lungenalveolen, Centralbl. f. allg. Pathol. u. path. Anat., 1933, lvi, 81-88

ETIOLOGY OF THE PULMONARY FIBROSES AND MEDICO-LEGAL ASPECTS OF PNEUMONOKONIOSIS

By WM S McCANN, M D , F A C P , *Rochester, New York*

THE medico-legal questions which have arisen in connection with the pneumonokonioses are of two kinds those which come from common law suits for negligence, and those which are connected with workmen's compensation laws Many of our states have not yet included pneumonokoniosis in their compensation schedules In these states a furious battle is being fought in the courts, into which medical men are being drawn by both sides The physician who is suddenly projected into the "no man's land," which is the territory of the expert medical witness, finds himself between two fires He is faced with ethical problems of the greatest complexity, bewildered and entangled by the barbed wire maze of legal technicalities, apt to fall in the slippery mud of legal chicanery It is the aim of the writer, on this occasion, to attempt to find the way by means of which the medical man may extricate himself without dishonor He must not, however, be content with this negative virtue He must go farther in a positive direction in an effort to mold and guide legal ethics, and to aid in setting up new laws and procedures for the better establishment of equity He must aid and guide industry in limiting at the source the causes for legal action

In a negligence action the plaintiff should be required to prove two things first, that he has sustained an injury, second, that this injury is the result of the negligence of the defendant In such actions the medical witness may play one of two rôles He is most frequently called upon to contribute his opinion as to whether or not an injury has been sustained In rare instances he may be qualified to give expert opinion as an industrial hygienist or sanitarian on the question of negligence Too frequently a medical witness is permitted to give an opinion on the question of negligence when he is inadequately qualified to give it Most of the ethical difficulties of the medical witness can be eliminated if he will observe two rules first, to refuse to give an opinion on matters which lie outside the field of his actual experience as an expert, second, to refuse to give an opinion on a hypothetical question in which the premises or assumptions are insufficiently exact to warrant the formation of a conclusion

When the medical witness is called upon for an opinion as to the nature and extent of injury to the lungs which may be attributed to the inhalation

* Read at the Philadelphia meeting of the American College of Physicians, April 30 1935

From the Department of Medicine, University of Rochester, School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals

of dust, there is available for his guidance a considerable amount of accurate information (Klotz ¹¹) The work of the experimental pathologists has given a clear picture of the evolution of pulmonary fibrosis resulting from exposure to dusts of various kinds, with accurate specifications as to concentration, duration, particle size, etc Similarly certain industries, notably that of gold mining, in which fairly pure silica is the principal noxious agent, have had a health hazard which can be rather specifically defined The injuries sustained in these industries result eventually in a fairly clear-cut nodular fibrosis, which presents a highly characteristic appearance to the pathologist or roentgenologist The "ambulance chasing" lawyers, however, have not confined their attention to these highly specific injuries Suits are filed against industries in which dusts of all kinds are found, organic as well as inorganic In many of these industries the nature of the dust hazard has not yet been clearly defined Work in progress in many centers indicates that the hazard varies tremendously, that some dusts are not only quite innocuous, but even protective in their action as in the case of gypsum, sea coal, aluminum oxide and certain clays (Gardner ^{5, 6})

The plaintiff's attorney is very rarely able to adduce evidence either of the quantity or composition of the dust, or of the particle size The dust is usually described in vague and general terms Statements are given as to its effect on the visibility of objects in the room, the amount settling out, on clothes, face, machinery, beams, etc In consequence when the plaintiff's case is complete the assumptions in hypothetical questions based upon it are frequently inadequate to justify an opinion as to the competency of the conditions described to produce the injuries alleged to exist

The defense in these actions may or may not possess data as to dust counts, petrographic and chemical analyses, roentgen-ray spectrum analyses When these data are available they are sometimes suppressed There is rarely time, in the preparation for trial to submit the question to the experimental pathologist for settlement In such cases some indication of the pathogenic possibilities in a dusty trade, concerning which other data are lacking, may be obtained by making a roentgen-ray survey of the men employed in it For instance, roentgen-ray examinations were made of the chests of 673 men applicants for reemployment, of whom 156 were foundry men and 517 a general group of industrial employees including some workers having had dust exposures of a hazardous nature, such as enamelling, sand blasting, chipping and grinding, but a majority of the general group were not exposed to recognized dust hazards The following is a crude analysis of the findings in this group

Group	Foundry		Non-foundry	
	No	Per Cent	No	Per Cent
Total	156		517	
Pneumonokoniosis	21	13.46	22	4.25
Active pulmonary tuberculosis	4	2.56	7	1.35
Healed pulmonary tuberculosis	11	7.05	39	7.54
Non-tuberculous respiratory infections	16	10.25	86	16.63
Other abnormalities	22	14.10	62	11.99
Normal		52.54	301	58.20

From the foregoing figures it is quite apparent that pneumokoniosis develops in a considerable number of foundry workers after long exposure, in the foregoing series after an average employment of about 17 years. Our experience leads us to believe, however, that the dust hazards in a foundry are not so great as those which exist in some other industries or occupations (gold mining, sand blasting). This may be due to the fact that dust concentrations are not so great, or to the admixture of other constituents in the dust which modify the action of pure SiO_2 . Against the 17 years required to produce pneumokoniosis in a foundry we can compare the 9 to 12 years required to produce silicosis in the gold miners of South Africa (Fraser and Irvine⁴). While the figures show a definitely greater incidence of active tuberculosis in this group of foundry workers as compared with the larger general industrial group our experience does not indicate that the tuberculosis hazard in foundries is nearly as great as that reported for some of the other dusty trades. We have observed not infrequently the healing of tuberculosis in men during the earlier stages of foundry pneumokoniosis. It is true, of course, that tuberculosis tends to become inevitably progressive in the nodular stages. Lanza and Vane¹² give statistics which show that the general mortality of foundry men is 55 per cent above the expected, and their mortality from tuberculosis 79 per cent above the expectancy, but these figures are low when compared with those of gold, silver, lead, zinc, and copper miners among whom the mortality from tuberculosis is from 8 to 18 times the general expectancy.

Collis and Yule³ present a most startling comparison of the general mortality experience in a group of workers in silica dust with that of a standard population and a group of workers not exposed to silica. Their analysis shows not only a great excess mortality from tuberculosis and all other respiratory diseases among the silica workers, but an extra mortality from such apparently unrelated causes as cancer, cerebral hemorrhage, cirrhosis of the liver and valvular heart disease as well. These findings lead Collis and Yule to the conclusion that "silica is such a body poison as is lead even though it exerts its maleficent influence, especially with regard to tuberculosis, mainly on the respiratory organs through which it gains access to the body."

Such general statements in regard to the most severe silicotic injuries, when placed before a jury may give quite an erroneous impression of the seriousness of the hazard in the foundry industry or in gypsum miners or in other dusty occupations in which the health hazard is relatively small. Data of the sort introduced by Lanza and Vane¹² are of the utmost importance to the medical witness in forming his opinion as to the competency of a given exposure to produce the injury claimed. The witness must on the other hand keep clearly in mind that the common law suit deals with an individual case, and not with a whole population submitted to analysis by an actuary.

The relationship of non-tuberculous infections to dust in the production

of pulmonary fibrosis is not as clear as that of tuberculosis. One reason for this, no doubt, is their lack of specificity and the difficulty of producing or controlling them in experimental animals. From the studies of McConnell and Fehnel¹⁴ and Collis and Yule³ it appears that the death rates for all non-tuberculous infections are higher among workers in siliceous dusts



FIG 1 Roentgenograph made of the lungs of S. B., October 12, 1929, during the second attack of acute respiratory infection. He had been employed as a sandblaster from 1920-1929.

than in the general population. In the roentgen-ray survey of 673 men to which we have previously referred, that type of fibrosis of the lower portions of the lungs such as is commonly seen in individuals suffering from chronic bronchitis or chronic upper respiratory infections, occurred more commonly in the non-foundry group. The number of men in the survey is too small to make the figures absolutely reliable. They suggest, however, that the worker in silica more frequently succumbs to acute pulmonary infections instead of surviving with chronic infections producing fibrosis.

Proske¹⁷ has presented a bacteriological study of some of the non-tuberculous infections occurring in pneumoconiosis, dealing largely with the anaerobic fuso-spirillar organisms.

An interesting case illustrating the rôle played by a recurring non-tuberculous infection in the evolution of a nodular fibrosis is that of S B, a man of 52, who was employed during the years 1920-1929 as a sand-blaster in a stove factory. Beginning in the spring of 1929 he had the first

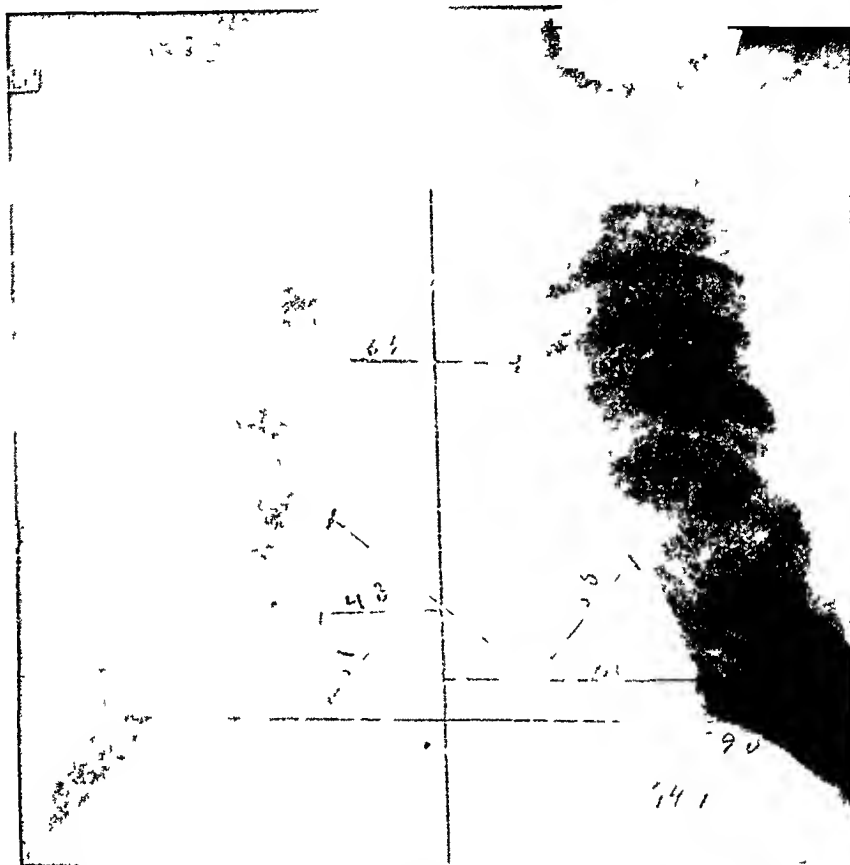


FIG 2 Roentgenograph made one month after figure 1, the signs of infection having subsided

of a series of severe respiratory infections with fever, leukocytosis, purulent sputum. In October 1929 he had the second attack of this type. The roentgenograph of his chest at that time is shown in figure 1, revealing diffuse soft nodular shadows in both lungs with dense confluence at the bases. Figure 2 shows the roentgenograph made one month later when the infection had subsided and all physical signs had disappeared. The roentgenograph reveals only a diffuse increase in the perivascular peribronchial markings with the faintest suggestion of nodulation. In January 1932 a third attack of acute respiratory infection occurred. In figure 3, the roentgenograph reveals dense shadows of consolidation in both lower lobes. Figure 4 is the roentgenograph made in October 1934 during an interval of freedom from evidences of infection. It reveals a considerable increase in the density of the peribronchial perivascular shadows and dense shadows in both hilus regions and right base.

In January 1934 the roentgenograph shown in figure 5 was made during an interval of freedom from acute infection. This shows an increase in the nodular shadows diffusely distributed through both lungs, though more dense in the bases.



FIG. 3. Roentgenograph made of chest of S. B. on January 9, 1932, fourteen months after figure 2, during third attack of acute respiratory infection.

In March 1934 another attack of pneumonia occurred. Figure 6 reveals a dense area of consolidation at the right lung base.

In March 1935 the patient was free of acute respiratory infection. The roentgenograph (figure 7) made at that time reveals a diffuse nodular fibrosis consistent with a diagnosis of silicosis. The evolution of this fibrosis occurred over a period of six years, during which four separate attacks of bronchopneumonia occurred. In each attack repeated examinations of the sputa failed to reveal tubercle bacilli.

If this case were in litigation, with only the occupational history, clinical and roentgenological findings upon which to base an opinion, a diagnosis of pneumoconiosis complicated by chronic respiratory infection could be made with "reasonable medical certainty." Such an opinion might be modified, however, if an autopsy were performed, in which sections were

subjected to micro-incineration by a technic such as that of Irwin¹⁰ in addition to the usual stained preparations. The data should also include chemical study of the ash of the lung. McNally¹⁵ has collected data on ash analyses from the literature and his own findings, which show that a value

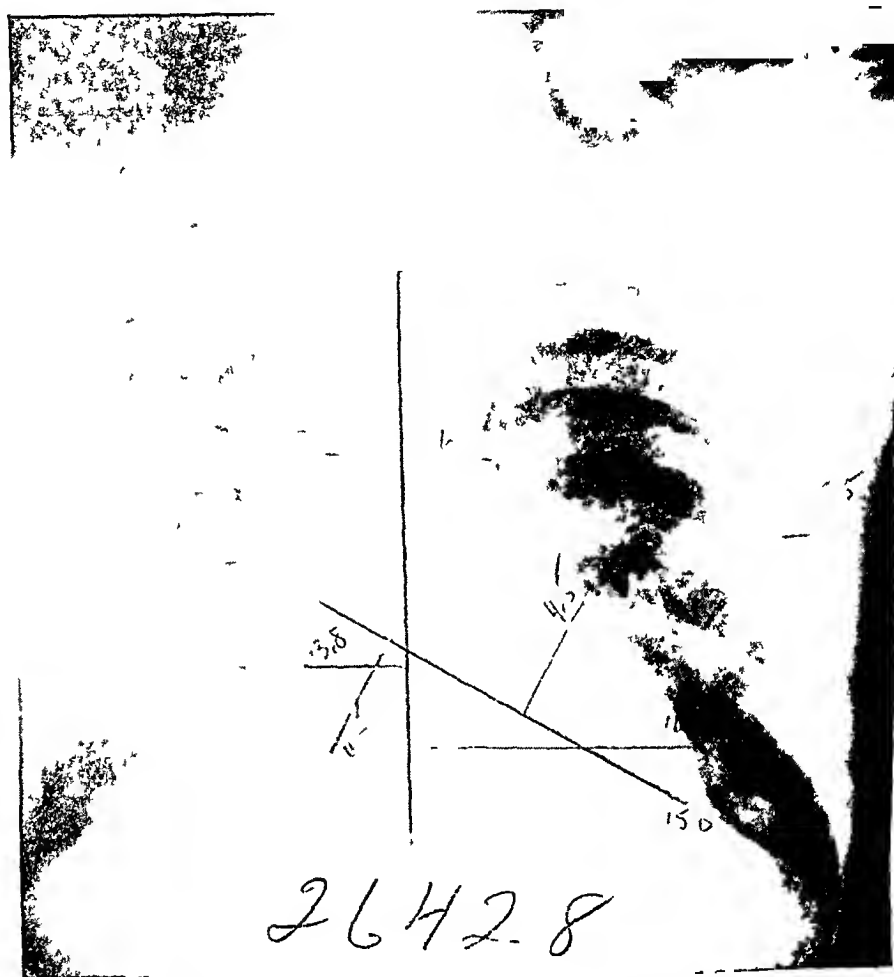


FIG 4 Roentgenograph of chest of S B, made October 24, 1932, during a period of quiescence of infection

of more than 2 mg SiO_2 per gram of dried tissue indicates undue exposure to dust. Silica determined chemically in this way may have been derived in part from silicates. For this reason chemical analysis of the ash should be supplemented by petrographic examination, and in addition to roentgen-ray spectrum analysis as described by Bale and Fray,¹ which gives a roughly quantitative estimate of the amount of free silica and of the silicates present.

The medico-legal problems of pneumonokoniosis under Workmen's Compensation are very different from those of the common law. In the Province of Ontario and in Wisconsin compensation may be adjusted to the degree of disability incurred. The problem of finding a yardstick for

the measurement of disability has been under active investigation at the University of Rochester for three years, and it is still far from solution. From observations of the pulmonary capacity and its subdivisions, and of the ventilation during exercise^{7, 8, 13} we may say that simple fibrosis comparable

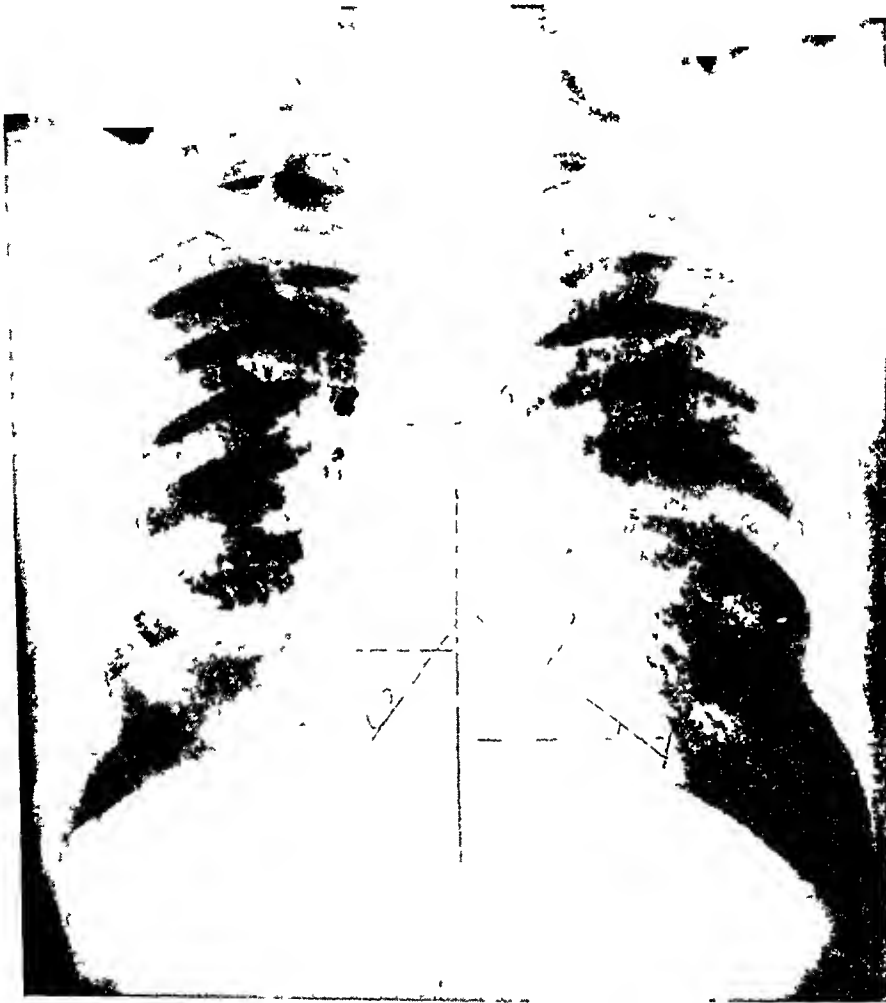


FIG 5 Roentgenograph of chest of S. B., January 1934, made during a period of freedom from infection. Nodular fibrosis has become more distinct.

to the primary stage of simple silicosis is not disabling. In the second stage of uncomplicated nodular fibrosis, there is practically speaking no disability for ordinary manual work if allowance is made for age. In our observations the subjects with nodular fibrosis had an average age of 47, while that of the normal controls with which they were compared was 23 years. If emphysema is added to the fibrosis, either by the intercurrent of asthma or in compensation for the shrinkage of a part of the lung in dense fibrous agglomerations, disability is greatly increased. It may fairly be

rated at 100 per cent when the residual air reaches 50 per cent of the total capacity

The demonstration of active tuberculosis at any stage should justify the award of compensation for total disability. In the case of primary pneu-



FIG 6 Roentgenograph of chest of S B, March 1934, during the fourth attack of acute respiratory infection five years after the first attack

monokoniosis of foundry workers, or iron miners, this may not be permanent, as tuberculosis may heal in this stage under appropriate treatment

In the age groups in which pneumokoniosis is most frequently found, cardiovascular disease becomes increasingly frequent, and such disease may contribute to the production of dyspnea. When this factor is detected by the clinical or electrocardiographic examinations it is impossible to determine the relative contributions of respiratory and cardiac lesions to the disability. However, if the viewpoint of Collis and Yule³ is accepted, namely, that silica is a general body poison as is lead, the differentiation between the two causes of respiratory disability, when they coexist, becomes less important

in achieving equity in compensation awards. This would be true particularly if cognizance were taken only of the extra hazard due to the occupation, so that compensation for complete disability were awarded in the ratio



FIG 7 Roentgenograph of chest of S B, March 1935, six years after the onset of acute respiratory infections, during an interval of freedom from acute symptoms

of the extra mortality above standard expectancy to total mortality for the workman's age group in his particular occupation

CONCLUSION

In this rambling discussion I have endeavored to show the complexity of the medico-legal aspects of pneumonokoniosis which makes it so difficult to secure equity under the common law in negligence actions. Pure pneumonokoniosis probably does not exist outside of laboratories. The fibroses of the lungs of workers in dusty trades are probably the result of a combined action of dust and of infection, non-tuberculous as well as tuberculous. It is extremely difficult to establish the responsibility for negligence in individual cases. Equity is more likely to be achieved through workmen's com-

pensation under a general occupational disease law in which awards are adjusted to the degree of disability

BIBLIOGRAPHY

- 1 BALE, W F, and FRAY, W A method for the analysis of dust samples employing x-ray diffraction, *Jr Indust Hyg*, 1935, *xvii*, 1
- 2 BOWMAN, P G, and BIANCO, A J Tularemic pneumonia, *ANN INT MED*, 1934, *vii*, 1491
- 3 COLLIS, E L, and YULE, G U Mortality experience of occupational group exposed to silica dust, compared with that of general population and occupational group exposed to dust not containing silica, *Jr Indust Hyg*, 1933, *xv*, 395-417
- 4 FRASER, D S, and IRVING L G Statistical account of the incidence and progression of silicosis among the gold miners of the Witwaters Rand, *Silicosis*, International Labor Office, Geneva, 1930, p 618
- 5 GARDNER, L U, and CUMMINGS, D E Reaction to fine and medium sized quartz and aluminum oxide particles, silicotic cirrhosis of liver, *Am Jr Path*, 1933, *ix*, 751-764
- 6 GARDNER, L U, CUMMINGS, D E, and DOWD, G R Experimental inhalation of bituminous coal dust and its effects upon primary tuberculous infection in guinea pigs, *Jr Indust Hyg*, 1933, *xv*, 456-465
- 7 HURTADO, A, KALTREIDER N L, FRAY, W W, BROOKS, W D W, and MCCANN, W S Studies of the total pulmonary capacity and its subdivisions VIII Observations on cases of pulmonary fibrosis, *Jr Clin Invest* 1935, *xiv*, 81
- 8 HURTADO, A, KALTREIDER, N L, and MCCANN, W S Studies of total pulmonary capacity and its subdivisions IX Relationship of oxygen saturation and carbon dioxide content of arterial blood, *Jr Clin Invest*, 1935, *xiv*, 94-105
- 9 IRWIN, D A Microincineration as an aid in diagnosis of silicosis, *Canad Med Assoc Jr*, 1934, *xxxi* 140-143
- 10 IRWIN D A Histological demonstration of siliceous material by microincineration, *Canad Med Assoc Jr*, 1934, *xxxi*, 135-140.
- 11 KLOTZ, O The pathology of pneumonokoniosis a review, *Am Jr Med Sci*, 1934, *clxxviii*, 418
- 12 LANZA, A J, and VANE, R J Prevalence of silicosis in the general population and its effects upon the incidence of tuberculosis, *Am Rev Tuberc*, 1934, *xxix*, 8-16
- 13 MCCANN, W S, HURTADO, A, KALTREIDER, N, and FRAY, W W Estimation of functional disability in pulmonary fibroses, *Jr Am Med Assoc*, 1934, *cii*, 810-815
- 14 McCONNELL, W J, and FEHNEL, J W Health hazards in foundry industry, *Jr Indust Hyg*, 1934, *xvi*, 227-251
- 15 McNALLY, W D Silicon dioxide content of lungs in health and disease, *Jr Am Med Assoc*, 1933, *ci*, 584-587
- 16 PANCOAST, H K, and PENDERGRASS, E P Roentgenologic aspect of pneumonokoniosis and its differential diagnosis, *Jr Am Med Assoc*, 1933, *ci*, 587-591
- 17 PROSKE, H O, and SAYERS, R R Pulmonary infection in pneumonokoniosis, bacteriologic and experimental study, *Public Health Rep*, 1934, *xliix*, 839-858

TREATMENT OF CHRONIC RHEUMATOID ARTHRITIS, FURTHER OBSERVATIONS ON THE USE OF STREPTOCOCCAL VACCINE ¹

By CHARLES W WAINWRIGHT, M D , F A C P ,
Baltimore, Maryland

IN a previous communication I ¹ have reported the results of attempts to confirm the blood culture studies of Cecil, Nicholls and Stainsby ² in cases of chronic rheumatoid arthritis. The technic of these investigators was followed in detail except for two minor variations which were devised to lessen the chances of contamination. In but a single instance were streptococci recovered from either the blood stream or the joint fluids so cultured. These results did not substantiate those of Cecil, Nicholls and Stainsby and others, who report the presence of streptococci in the blood stream of 50 per cent or more of cases of chronic rheumatoid arthritis. They agree, however, with the observations of Dawson, Olmstead and Boots ³ and others, who failed to recover streptococci from either the blood stream or from joint fluid with sufficient frequency to be of significance. This lack of uniformity in the results obtained by different observers leaves us in doubt about the frequency with which streptococci occur in the blood stream of patients with chronic rheumatoid arthritis, and makes it impossible conclusively to maintain that the joint reaction in this disease is a focal or metastatic lesion. This does not mean that the streptococcus plays no part in the pathogenesis of the disease or even that it may not be the chief cause, but merely puts in question the manner in which the joint reaction is produced.

That the streptococcus is associated with chronic rheumatoid arthritis is indicated by the results of agglutination tests. Agglutinins for hemolytic streptococci have been found in the sera of patients suffering from this disease by all investigators who have searched for them. Dawson, Olmstead and Boots ³ found them in 67 per cent of 157 cases, in dilutions varying from 1 to 20 to 1 to 2560. Nicholls and Stainsby ⁵ found agglutinins for their "typical strain" in practically all patients with chronic rheumatoid arthritis. I have reported the study of 51 cases in which 46, or 90 per cent, showed agglutinins for hemolytic streptococci when tested against AB₁, a "typical strain" obtained from Cecil, Nicholls and Stainsby, and against the scarlet strain NY₆. Since this report I have increased the number of cases studied to 87. I have found that the same proportion gives positive results, having demonstrated agglutinins for AB₁ and NY₆ in 79, or 90 per cent, of the 87 cases.

In a previous article I reported the occurrence of positive skin reactions in 55 cases of chronic rheumatoid arthritis tested intracutaneously with salt

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935

solution suspensions of heat-killed streptococci. In these, 49, or 90 per cent, reacted maximally to a hemolytic strain, whereas only 6, or 10 per cent, gave the maximum reaction to a green strain. The number of cases tested for their skin reactions to streptococci has now been increased to 78. Table 1 gives the results and includes also the skin reactions in 11 cases of combined arthritis, 10 cases of hypertrophic arthritis and 3 cases of Still's disease.

TABLE I
Skin Reactions to Intracutaneous Injections of Hemolytic and Green Streptococci

	No giving negative reactions	Reacting to 1 strain	Reacting to 2 strains	Reacting to 3 strains	Reacting to 4 strains	Reacting to 5 or more	Total
Rheumatoid Arthritis	3	14	8	13	15	25	78
Combined Arthritis	3	1	1	2	2	2	11
Hypertrophic Arthritis	4	1	1	2	—	3	10
Still's Disease	2	—	—	—	—	1	3

Cases of Chronic Rheumatoid Arthritis Showing		
Maximal skin reaction to hemolytic streptococci		69
Maximal skin reaction of viridans streptococci		6
No skin reaction		3
Total		<u>78</u>

Having demonstrated the strain of streptococcus among the many used to which a patient was most skin sensitive, this information was used as a guide to vaccine treatment. Twenty-eight patients with chronic rheumatoid arthritis received streptococcal vaccine intravenously at weekly intervals for periods varying from two months to over one year. The results of treatment were reported in the previous publication, and since then 17 additional patients have been treated. The present report will deal with the results of treatment in this group of 45 patients.

The group comprises 40 cases of chronic rheumatoid arthritis and 5 cases of combined arthritis in which the evidences of rheumatoid arthritis predominated. In every instance all foci of infection were removed and sufficient time was allowed to elapse to be sure that no benefit or further benefit was to be derived from the removal of the infections. The disease had been present for not less than 6 months, the average duration of all cases being 18 months, a sufficient length of time to justify classing them as chronic arthritis. Of the 45 patients, 30, or 67 per cent, have shown evidence of improvement, 15, or 33 per cent, have shown no clearly demonstrable improvement.

Because of the predominance of positive skin reactions to hemolytic strains of the streptococcus the vaccines which were used were prepared from hemolytic strains in all but two instances. Ten strains of hemolytic streptococcus derived from different sources were used. In 11 cases "Marth" strain obtained from a case of hemolytic streptococcus septicemia

was used, in 10 cases, NY₆, a scarlet strain, in 6 cases the "Lee" strain, obtained from a case of hemolytic streptococcus septicemia with acute infectious arthritis, in 6 cases AB₁, a "typical strain" furnished us by Cecil, Nicholls and Stainsby, in 3 cases "James," a scarlet strain, and in 3 "Cotton," a strain obtained from a case of hemolytic streptococcus septicemia. In one case each, "Evans," a scarlet strain, "Schmedes," "Altomare" and "Birge," strains from unknown sources, were used. The viridans strains used were "Tschetter," obtained from a knee joint, and "Waller" from an unknown source.

The patients have received weekly intravenous injections of vaccine prepared from the strain to which they had shown the maximal skin sensitivity. The initial dose was approximately 5 million organisms contained in 0.5 c.c. of vaccine. The dose was increased by 0.5 c.c., provided no constitutional reaction occurred. Febrile reactions were avoided by beginning with a small dose and increasing the dose sufficiently slowly. The increase in dosage was gauged by the patient's response and no set schedule of dosage was followed. In some instances fever did come on after the first few injections, but the subsequent doses were sufficiently reduced to prevent further reactions. Although no constitutional reactions occurred, as a rule the patients complained of focal reactions for about 24 hours after each injection. This reaction was manifested by increased pain in the involved joints, but after the reaction subsided the symptoms were usually improved. The improvement experienced always came about slowly, as a rule making its appearance in from four to six weeks after treatment was begun. In some instances it progressed more rapidly than in others, but often was not a steady improvement. From time to time during treatment joints have flared up but would often subside in a shorter time than was the patient's previous experience with exacerbations of such degree. In some cases definite improvement has been observed up to a point at which the arthritis seemed to become stationary, and beyond this point no further improvement was obtained. The benefit derived manifested itself by decreased pain, reduced swelling of the joints and surrounding soft tissues, and increased mobility of the joints. We have seen fusiform fingers diminish greatly in size and the swelling of other involved joints also decrease. In two instances improvement was in progress when the treatment was interrupted, in one instance because of the development of pulmonary tuberculosis with large hemoptyses, and in the other because of a cerebral thrombosis which produced a right hemiplegia. In both cases an exacerbation of the arthritis followed. Subsequently treatment was begun again and in each case improvement once more occurred. In the first instance much more improvement followed the second course of treatment than had followed the first, in the second instance an equal degree of improvement followed both.

Streptococcal vaccine was given intravenously to two patients suffering from active pulmonary tuberculosis. The increase in dosage was made very cautiously and constitutional reactions were entirely avoided. In both cases

the arthritis has improved during treatment and in one case improvement has been more striking than in any other case in the series. The pulmonary tuberculosis not only has not progressed but healing has gone on, and in one case the pulmonary lesion now is considered to be inactive.

During treatment the skin reaction to the strain used has regularly diminished in intensity and in most instances has entirely disappeared. Furthermore, agglutinins have appeared in the patient's sera for the strain employed, when not already present, and when present, as was the case with the hemolytic strains, the titre has materially increased during treatment.

One case improved during treatment to such an extent that the joints were considered inactive. Destructive change had not taken place. The previously affected joints appeared objectively normal and the patient was having no symptoms. The skin reaction, which originally was an area of erythema 2.25 cm in diameter with a central area of induration of 0.5 cm, became quite negative. During treatment the patient had developed agglutinins for the strain used to a dilution of 1-5120. It seemed advisable to discontinue treatment. Three months later there was an exacerbation of the arthritic process and the sedimentation rate was then 51 mm in one hour. Furthermore, the skin reaction to the strain used, completely negative three months before, now reappeared and was an area of erythema 1.5 cm in diameter. Further treatment of this case has only just begun and we do not know what results may follow.

In all of the cases treated the sedimentation rate has been elevated, in some much higher than in others. The highest rate at the beginning of treatment was 54 mm in one hour and the lowest was 15 mm. In 19 cases we have had the opportunity to follow the sedimentation rate during treatment and in this small series our observations have not been conclusive. In one of the most active cases, a man with every finger on each hand fusiform and inflamed and with both ankles actively involved, the rate was 17 mm in one hour when treatment was started. There has been decided improvement in the ankles and the fusiform swelling of the fingers has diminished somewhat in size, yet the sedimentation rate has varied between 13 mm and 22 mm in one hour and is now 13 mm. In others the rate has steadily dropped with improvement as might be expected. This was observed in 12 instances. In others there has been an initial drop with a secondary rise, usually not to the original level, and in still others there has been no reduction whatever in the elevated sedimentation rate, although both subjective and objective improvement occurred. In the cases which have not improved the rate has not varied from its initial elevated level.

Fifteen of the 45 cases treated either have not improved or else the change which has come about has been so slight that improvement was questionable. In this group are three cases of combined arthritis, five cases showed longstanding and extensive change involving many joints, in seven cases we thought it reasonable to expect improvement but thus far none has come. In none of the cases has the arthritis been made worse.

by treatment and no untoward reactions have occurred. In a few instances the urine has been followed after the injection of vaccine and in none has there been any evidence whatsoever of irritation of the kidney.

TABLE II
Cases Treated with Streptococcal Vaccine

	No of cases	Improved	Unimproved
Rheumatoid Arthritis	40	28 (70%)	12 (30%)
Combined Arthritis	5	2 (40%)	3 (60%)

COMMENT

The attempt has been made to influence the joint reaction in chronic rheumatoid arthritis by the intravenous injection of streptococcal vaccine. This bacterial group was selected by reason of the universally demonstrated ability of the sera of chronic arthritics of the rheumatoid type to agglutinate hemolytic strains of streptococci. Just what this reaction may imply we cannot definitely say at this time but it cannot be entirely without significance. It is unlikely that natural agglutinins¹ would be so strikingly congregated as we find them in this type of arthritis, whereas they are found only infrequently in individuals suffering from other diseases and in normal people. I have found the reaction particularly useful in the differentiation of hypertrophic from rheumatoid arthritis and in establishing the existence of a rheumatoid arthritis when combined with hypertrophic arthritis. Keefer; Myers and Oppel² have shown that the agglutinating substances are contained in the proper globulin fraction of the serum and that they are true agglutinins. It seems to me that the almost uniform demonstration of this agglutinating property of the sera of patients suffering from chronic rheumatoid arthritis is the most convincing evidence yet produced to incriminate the streptococcus of playing a role in the etiology of the disease. On the other hand, Myers, Keefer and Holmes³ have found that rheumatoid arthritis is not accompanied by an increase in the antifibrinolytic property of the plasma as is observed following proved hemolytic streptococcal infections and in rheumatic fever, and one hesitates to state emphatically that the presence of agglutinins indicates a causal relationship when the organism can be isolated so infrequently from patients with rheumatoid arthritis and when no other direct connection can be established. Just what the relation is must await further study. At the present time I am investigating whether or not the presence of agglutinins in arthritic sera for hemolytic streptococci is confined to human strains or can be demonstrated for the other groups of Lancefield's classification.

Since the agglutination of hemolytic streptococci occurred too frequently in this disease to be regarded as an accidental association we proceeded to test chronic arthritics for evidences of sensitivity to streptococci. We found that not only was the patient with this disease skin sensitive to streptococci but that this sensitivity was much more pronounced for hemo-

lytic streptococci than for green strains. Ninety per cent gave the maximal skin reaction to the former and 10 per cent to the latter. We have not compared this with the skin reactions of non-arthritis. We wished merely to learn to what strain of streptococcus the given arthritis was most sensitive when he showed agglutinins in his blood serum for hemolytic strains of this bacterial group. The demonstration of skin sensitivity does not of necessity indicate either a joint sensitivity or a general sensitivity, but in each case we have observed the skin reaction to diminish during treatment and in most instances to disappear entirely. The observation that the skin reaction reappeared in one case during a recurrence of symptoms after treatment had been stopped may be of far-reaching significance if this occurrence is found regularly under these circumstances.

In treating these cases we wished to see what relation might exist between the diminution of sensitivity to streptococci, as demonstrated by a decrease in the intensity of the skin reaction, and the manifestations in the joints. Not only has the skin reaction diminished during treatment but the agglutinating power of the patient's serum for the organism used has increased. In the cases showing improvement these changes have occurred concomitantly with improvement in the joints. We do not pretend to say that this relation establishes the specificity of the joint reaction. In the cases failing to show improvement under treatment there has been no difficulty in developing agglutinins or in raising their titre when a hemolytic strain was used, and in these the skin reaction also diminished. The benefit derived may be due to a non-specific reaction. We have however, eliminated the febrile reaction, to which is commonly attributed the benefit resulting from the usual forms of non-specific vaccine therapy. We have attempted to desensitize the arthritis to the strain of streptococcus to which he showed the greatest sensitiveness. Furthermore, the strain used belonged to that group of bacteria for which the patient possessed agglutinins in his serum. And when this property of his serum indicates so definitely some relation of streptococci to his disease although the nature of this relation is unknown an alteration of this sensitivity could reasonably affect his arthritis. It is entirely possible that the steady increase in dosage is not necessary, but in all cases we have regularly increased the dose, keeping below the point at which constitutional reactions were produced. I do feel that the long continued use of vaccine is of value and have not hesitated to treat some cases for more than a year.

The group in which I have been able to follow the sedimentation rate is small but the results obtained are confusing. A diminution in rate with improvement or an unaffected rate in cases failing to show improvement would seem logical, but the bizarre findings would tend to cause one to doubt the value of the test as a guide to improvement. I have not found it necessary to resort to this test to determine whether or not improvement had occurred but have attempted to confirm the clinical evidence of im-

provement by its use. Certainly we are dealing with a test which is subject to many variables and we have thus far found it of doubtful value.

SUMMARY

1 Seventy-nine of 87 cases of chronic rheumatoid arthritis were found to have agglutinins for hemolytic streptococci in their sera

2 Seventy-five of 78 cases of chronic rheumatoid arthritis showed skin reactions to one or more strains of streptococci

3 Sixty-nine cases, or 88 per cent, showed the maximal reaction to hemolytic strains, whereas 6 cases, or 7.7 per cent, showed the maximal reaction to viridans strains. Three cases showed no skin reactions to streptococci

4 Thirty of 45 cases of chronic rheumatoid arthritis have shown improvement when treated with vaccine prepared from the strain to which they were most skin sensitive

BIBLIOGRAPHY

- 1 WAINWRIGHT, C. W. Treatment of chronic rheumatoid arthritis with streptococcus vaccine on basis of skin sensitivity, *Jr Am Med Assoc*, 1934, ciii, 1357-1361
- 2 CECIL, R. L., NICHOLLS, E. E., and STAINSBY, W. J. Bacteriology of blood and joints in chronic infectious arthritis, *Arch Int Med*, 1929, xliii, 571-605
- 3 DAWSON, M. H., OLMSTEAD, M., and BOOTS, R. H. Bacteriologic investigations on blood, synovial fluid and subcutaneous nodules in rheumatoid (chronic infectious) arthritis, *Arch Int Med*, 1932, xlix, 173-180
- 4 DAWSON, M. H., OLMSTEAD, M., and BOOTS, R. H. Agglutination reactions in rheumatoid arthritis, *Jr Immunol*, 1932, xxi, 187-204
- 5 NICHOLLS, E. E., and STAINSBY, W. J. Streptococcal agglutinins in chronic infectious arthritis, *Jr Clin Invest*, 1931, x, 323-335
- 6 KEEFER, C. S., MYERS, W. K., and OPPFL, T. W. Streptococcal agglutinins with rheumatoid (atrophic) arthritis and acute rheumatic fever, *Jr Clin Invest*, 1933, xi, 267-277
- 7 MYERS, W. K., KEEFER, C. S., and HOLMFS, W. F., JR. Resistance to fibrinolytic activity of hemolytic streptococcus with special reference to patients with rheumatic fever and rheumatoid (atrophic) arthritis, *Jr Clin Invest*, 1935, xiv, 119-123

GASTRIC ACIDITY IN CHRONIC ARTHRITIS *

By EDWARD F HARTUNG, M D, and OTTO STEINBROCKER, M D,
New York, N Y

ACHLORHYDRIA and hypochlorhydria are frequently mentioned as accompaniments of chronic arthritis, but a search of the literature does not reveal any recent investigations of their occurrence in which the present technic including fractional analysis or the present standards of interpretation have been employed. There has, moreover, not been found any attempt to differentiate the gastric secretions in rheumatoid arthritis from those in osteoarthritis, although the present day division of arthritis into these two great groups would seem to make such a distinction of importance.

The object of this study was three-fold: to determine the gastric acidity in chronic arthritis by the fractional method, to compare the gastric acidity in rheumatoid and in osteoarthritis, and to determine the difference between the gastric acidity in arthritics and that in normal subjects.

Table 1 gives a summary of the previously published reports on gastric acidity in arthritis. In no study was the distinction made between rheumatoid and osteoarthritis. The incidence of achlorhydria found in these pub-

TABLE I
Published Reports on Gastric Analysis in Arthritis

	Method	Sex	No of Cases	Achlor-hydria per cent	Hypo-chlor-hydria per cent	Normal Acidity per cent	Hyper-chlor-hydria per cent
Woodward ⁴	E*	—	10	20	40	0	0
Faber ⁵	E	—	65	23	—	0	0
Lottrup ⁶	E	—	9	44	—	—	—
Bell ⁷	F†	—	13	38	23	14	23
Coates ¹	E	—	20	70	5	25	0
Venables ⁸	F	—	8	—	—	50	—
Douthwaite ²	F	—	30	0	0	90	—
Ashcroft ⁹	F	—	50	large proportion		0	—
Miller and Smith ¹⁰	F	F	170	24	7	—	—
Hurst ¹¹	F	M	80	17	6	—	—
	F	—	15	20	33	—	—

* E—Ewald test meal

† F—Fractional gastric analysis

lished reports varies from 70 per cent in Coates' ¹ to 0 per cent in Douthwaite's ². These results are difficult to interpret, but would tend to cause one to believe that until the publication of the work of Woodward ⁴ and Douthwaite ² the incidence of achlorhydria in arthritis was not properly appreciated.

* Received for publication April 22, 1935

From the Arthritis Clinic, Department of Medicine, New York School of Medicine, New York City.

there were no reliable figures for the incidence of achlorhydria in normal subjects at various ages. The incidence of achlorhydria is now known to increase with advancing years. Since osteoarthritis is more common in older individuals it may be seen that, if among the reported cases there happened to be an undue number of osteoarthritis, the high incidence of achlorhydria in such a series might be attributable not to arthritis but to the high average age of the patients. Probably all that can be inferred from these earlier papers is that achlorhydria is a common finding in arthritis.

METHOD

A group of 70 patients with chronic arthritis was studied. This group consisted of an equal number of subjects with osteoarthritis and rheumatoid arthritis. Only classical cases of each type were included. Fractional gastric analysis was performed on each patient before treatment was instituted.

The Rehfuess¹² method, somewhat modified, was employed. The tube was passed and a fasting specimen obtained. Eight ounces of "Cream of Wheat," cooked with water, were then given. After this feeding 10 c c of the gastric content were extracted every 15 minutes. Each specimen was titrated against tenth-normal sodium hydroxide. Topfer's reagent was used as the indicator. Histamine was administered as a gastric stimulant in a few of the analyses. We did not think it important for the purposes of this study to use it as a routine procedure.

RESULTS

In estimating the results of our analyses the standards of Bell⁷ were followed. These are somewhat at variance with those of other writers, but seem most applicable here. The previous studies of arthritis summarized in table 1 which we are comparing with our own figures, were also based on Bell's standards. These are as follows:

1. Achlorhydria, in which free hydrochloric acid is present at no period of the analysis.

2. Hypochlorhydria, in which no fraction has contained free hydrochloric acid in excess of 10 units (0.0365 per cent hydrochloric acid).

1. *Gastric Acidity in Arthritis*. Table 2 gives the details of each analysis, and table 3 presents a synopsis of the results in our cases. All our cases were females. The general sex incidence in our clinic is about five females to one male. Analyzed according to the standards of Bell, we find the following results. The average age of patients with rheumatoid arthritis was 41 years, and of those with osteoarthritis, 52 years. The incidence of achlorhydria, nevertheless, was 28.6 per cent in the former group, compared with 25.7 per cent in the latter. The incidence of subacidity totalled 45.6 per cent in rheumatoid arthritis and 28.7 per cent in osteoarthritis. It is to be noted also from table 2 that the general trend toward increased acidity is greater in the osteoarthritis group.

TABLE II
Fractional Gastric Analysis in Rheumatoid and Osteoarthritis

Rheumatoid Arthritis 35 cases								Osteoarthritis 35 cases							
Number of case	Fast-ing	Minutes after Feeding						Number of case	Fast-ing	Minutes after Feeding					
		15	30	45	60	75	90			15	30	45	60	75	90
29	0*	0	0	0	0	0	0	27	0*	0	0	0	0	—	—
25	0	0	0	0	0	0	0	1	0	0	0	0	0	0	—
22	0	0	0	0	0	0	0	12	0	0	0	0	0	—	—
14	0	0	0	0	0	0	0	15	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	21	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	16	0	0	0	0	0	0	—
27	0	0	0	0	0	0	0	34	0	0	0	0	—	—	—
31	0	0	0	0	0	0	0	19	0	0	0	0	0	0	—
13	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	20	0	0	0	0	5	1	0
20	0	0	0	0	0	0	2	28	0	0	0	13	9	9	20
34	0	0	9	0	0	0	0	22	0	0	7	12	15	—	—
1	0	0	2	1	1	0	0	3	0	0	20	17	9	1	0
8	0	0	0	4	0	—	—	7	0	0	0	0	0	26	28
10	0	8	10	0	0	0	3	18	0	0	0	0	29	14	17
26	0	0	5	10	8	0	0	25	0	0	16	21	11	10	8
30	0	0	0	0	0	13	0	14	0	0	16	34	36	42	48
24	0	0	5	14	18	—	—	26	0	15	16	60	26	16	36
17	0	0	2	8	21	0	—	11	0	15	40	24	23	25	10
16	0	0	3	—	26	30	28	4	0	0	19	44	25	28	—
32	0	0	10	18	2	3	0	17	0	15	20	30	40	—	—
33	0	0	2	4	24	10	11	24	0	16	28	45	50	57	68
12	0	10	20	24	—	—	—	31	0	0	21	37	30	42	31
3	0	0	0	14	15	0	0	30	0	22	27	16	0	18	0
21	0	0	13	25	11	0	0	29	0	22	10	58	56	63	56
7	0	0	10	31	34	28	0	8	13	23	36	29	15	30	—
18	0	1	18	20	15	—	—	32	15	48	58	51	34	33	30
2	0	0	20	17	9	1	—	10	0	36	45	33	30	42	42
19	0	10	30	33	—	15	25	6	20	41	46	54	38	13	0
11	0	24	20	42	22	27	24	33	24	22	20	29	39	38	48
23	0	5	40	40	42	50	20	2	7	47	55	76	78	85	—
28	0	21	45	45	18	—	—	5	22	53	54	66	87	85	92
9	28	30	52	34	—	—	—	23	30	30	35	20	5	5	25
5	0	10	24	36	43	60	43	9	38	17	33	30	41	50	23
4	13	18	26	83	65	52	15	35	72	18	16	20	13	47	—

* HCl in terms of tenth normal sodium hydroxide

TABLE III
Summary of Results in Rheumatoid and Osteoarthritis

	Sex		Average age	Achlor-hydræ	Hypochlor-hydræ
	M	F			
Rheumatoid Arthritis (35 cases)		100%	41 yrs	28.6% (10 cases)	17% (6 cases)
Osteoarthritis (35 cases)		100%	52 yrs	25.7% (9 cases)	3% (1 case)

2 Comparison of Gastric Acidity in Arthritics with That in Normal Subjects It is now generally accepted that achlorhydria may occur in otherwise normal people, and that there is a steady increase in the incidence of this anacidity from youth to old age Vanzant et al³ of the Mayo Clinic made a study of the gastric analyses of 3,746 subjects who had been found free of any disease affecting the mucous membrane or secretory activity of the stomach Then data on the incidence of achlorhydria in this group appear in table 4 We are quoting only that part of their work relating to "true achlorhydria," where free acid did not appear either after repeated fractional analysis or after the injection of histamine

TABLE IV
Prevalence of True Achlorhydria *

Age in years	Males			Females		
	Cases	Per Cent	Total Cases	Cases	Per Cent	Total Cases
20-24	—	—	111	3	3.2	94
25-29	8	3.6	220	9	5.8	156
30-34	5	3.0	169	13	7.6	172
35-39	9	3.9	232	24	11.1	217
40-44	27	10.3	263	17	10.9	156
45-49	19	9.3	203	18	14.8	122
50-54	37	18.5	200	27	15.8	171
55-59	27	17.8	152	31	20.8	149
60-64	36	23.1	156	39	28.1	139
65-69	24	23.0	103	15	26.3	57
70-74	7	20.6	34	5	23.8	31
75-79	2	18.2	11			
Total	200	10.8	1,854	201	13.8	1,454

* After Vanzant et al³

Most of our cases of rheumatoid arthritis range between 30 and 50 years of age, the average being 41 years In Vanzant's group of normal females between these ages the average incidence of achlorhydria was 10.8 per cent This figure is much lower than the 28.6 per cent which we found in our series of rheumatoid arthritis Our group of osteoarthritis patients varied between 40 and 60, the average being 52 years In Vanzant's normals of this age, the incidence of achlorhydria was 15.5 per cent, whereas in our osteoarthritis the incidence was 25.7 per cent

In figures most comparable to Vanzant's, published by Sagal, Marks, and Kantor,¹³ summarizing the findings of gastric acid in 6,679 ambulatory gastrointestinal cases, we find that the incidence of achlorhydria from 30 to 50 years is 6.5 per cent, and from 40 to 60, 12 per cent

DISCUSSION

The status of gastric acidity in arthritis is important for a proper appreciation of the disease as a whole Although in the past opinions have

been held to the contrary, it is now generally accepted that achlorhydria, when found in arthritis, is a secondary factor and probably not directly related to the basic etiology of the disease. It is probably an attribute of the constitutional inadequacy so prominent in arthritis. Other conditions characterized by general debility are known to be associated with increased incidence of anacidity. In addition to the well-known variations of gastric acidity in gastrointestinal conditions, free hydrochloric acid is known to be absent or diminished at times in acute infectious diseases such as typhoid and paratyphoid, and after such acute infections as typhus, influenza, pneumonia, and enteritis. In malaria and pulmonary tuberculosis it has been noted that achlorhydria and hypochlorhydria become more common as the disease progresses. In addition to its presence in pernicious anemia where it may have a causal relationship to the etiology, achlorhydria has been found frequently in other chronic, debilitating diseases such as diabetes mellitus, hyperthyroidism, and pellagra.

It has been pointed out that high carbohydrate intake tends to lower gastric acidity. Large amounts of cane sugar (100 grams) or glucose in concentrated solution markedly depress gastric secretion and delay evacuation of the stomach. The high carbohydrate intake of pre-arthritis patients has received comment in the literature.

The rôle of the sympathetic nervous system in gastric secretion is probably important, and its function is known to be deranged in rheumatoid arthritis. Cannon¹⁴ states that in normal men and animals all painful stimuli cause some inhibition of the entire phase of gastric secretion, as do fear, anger, anxiety, and kindred emotions. For this reason, the continuous or sudden pain associated with arthritis may be an etiological factor in these gastric findings.

There still exists a dispute as to the mechanism of achlorhydria. The older idea was that achlorhydria is usually due to a gastritis of the chronic type and that the infection, possibly introduced with food, is generally blood-borne and secondary to disease in some other part of the body. More recently, it has been held that there is more evidence favoring the belief that it is a congenital condition. There may be a familial tendency.

The exact effect of achlorhydria on gastrointestinal function is not clear. Its responsibility as a cause of diarrhea is minimized today. Heath, Castle, and Strauss¹⁵ have shown that the intrinsic factor is not absent in achlorhydria except in the presence of pernicious anemia. It has been stated that a lack of acid in the stomach allows swallowed bacteria to enter the intestinal tract. Recent work of Furby and Arnold,¹⁶ however, throws doubt on the bactericidal powers of free hydrochloric acid in relation to stomach and intestinal bacteria.

Our studies lead us to believe that achlorhydria occurs frequently enough to be an important part of the clinical picture in chronic arthritis. In this condition the administration of hydrochloric acid appears to be of benefit when indicated by diminished gastric acidity.

CONCLUSIONS

1 In a group of 70 patients with chronic arthritis, achlorhydria occurred in 28.6 per cent of the cases with rheumatoid arthritis, and in 25.6 per cent of the cases with osteoarthritis, hypochlorhydria was detected in 17 per cent of the former and in 3 per cent of the latter.

2 The incidence of subacidity was greater in rheumatoid arthritis than in osteoarthritis, although the latter represented an older age group.

3 Achlorhydria and hypochlorhydria appeared with remarkably greater frequency in our group of arthritic patients than in normal subjects of the same age.

4 Subacidity appears with such frequency in chronic arthritis that it must be considered an important feature of the clinical picture of that disease.

BIBLIOGRAPHY

- 1 COATES, V, and GORDON, R. G. Differential diagnosis of rheumatoid arthritis as clinical entity, *Brit Med Jr*, 1923, *ii*, 561-563.
- 2 DOUTHWAITE, A. H. Clinical study of rheumatoid arthritis, *Brit Med Jr*, 1925, *i*, 1170-1172.
- 3 VANZANT, F. R, and others. Normal range of gastric acidity from youth to old age, analysis of 3746 records, *Arch Int Med*, 1932, *xliix*, 345-359.
- 4 WOODWARD, A. S, and WALLIS, R. L. M. The relation of the gastric secretion to rheumatoid arthritis, *Lancet*, 1912, *ii*, 942-944.
- 5 FABER, K. Anaemiske Tilstande ved den kroniske Achylia gastrica, *Berl klin Wchnschr*, 1913, *i*, 958-962.
- 6 LOTTRUP, M. C. Über chronische Arthritiden, Achylie und Anämie, *Ztschr f d ges phys Therap*, 1929, *xxxviii*, 10-16.
- 7 BELL, J. R. Notes on consecutive series of 425 gastric analyses by fractional method, *Guy's Hosp Rep*, 1922, *lxxii*, 302-314.
- 8 VENABLES, J. F, and KNOTT, F. A. Investigation of duodenal contents and bile in man, *Guy's Hosp Rep*, 1924, *lxxiv*, 245-255.
- 9 ASHCROFT, L. S, and others. Arthritis deformans, observations on its etiology and treatment, *Brit Med Jr*, 1925, *ii*, 13.
- 10 MILLER, S, and SMITH, F. B. Investigation of gastric function in chronic arthritis and fibrositis, *Quart Jr Med*, 1927, *xx*, 271-283.
- 11 HURST, A. F. Discussion on the etiology and treatment of osteoarthritis and rheumatoid arthritis, *Proc Roy Soc Med*, 1923-1924, *xvii*, 10.
- 12 REHFUSS, M. E, BERGEIM, O, and HAWK, P. B. Gastrointestinal studies. II. The fractional study of gastric digestion with a description of normal and pathologic curves, *Jr Am Med Assoc*, 1914, *lxiii*, 909-915.
- 13 SAGAL, Z, MARKS, J. A, and KANTOR, J. L. Clinical significance of gastric acidity, *ANN INT MED*, 1933, *vii*, 76-88.
- 14 CANNON, W. B. Bodily changes in pain, hunger, fear and rage, 1920, D. Appleton and Co, New York, p. 19.
- 15 HEATH, C. W, CASTLE, W. B, and STRAUSS, M. B. Quantitative aspects of iron deficiency in hypochromic anemia, parenteral administration of iron, *Jr Clin Invest*, 1932, *xi*, 1293-1312.
- 16 FURBY, S. F, and ARNOLD, L. Influence of gastric acid secretion upon the bactericidal power of gastrointestinal tract, *Proc Soc Exper Biol and Med*, 1931, *xxviii*, 372-374.

DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE LIVER

By B B VINCENT LION, F A C P, *Philadelphia, Pennsylvania*

AN adequate discussion of the differential diagnosis of liver disease would have to consider the following groups

- 1 Hepatitis toxic and infectious
- 2 Hepatocholangitis
- 3 Hepatic-intestinal toxemia
- 4 Simple hepatic cirrhosis
- 5 Pigmented cirrhosis with anthracosis
- 6 Cirrhosis with hemochromatosis
- 7 Kinnear-Wilson cirrhosis
- 8 So-called Banti's disease
- 9 So-called Tropical Liver
- 10 Cancer of the liver
- 11 Syphilis of the liver (relatively common)
- 12 Tuberculosis of the liver (comparatively rare)
- 13 Hydatid cysts (dog disease) and other cysts
- 14 Distomiasis or liver fluke (sheep or fish disease)
- 15 Trematode or other parasitic disease
- 16 Amebic abscess
- 17 Various bacterial abscesses
- 18 Acute fatty degeneration (chloroform, phosphorus, carbon tetrachloride, etc)
- 19 Acute yellow atrophy or acute necrosis (various arsenicals atophan, cinchophen, farastan, etc)
- 20 Acute ictero-hemorrhagic spirochetosis (Weil's disease)
- 21 Hemolytic jaundice with splenomegaly
- 22 So-called simple catarrhal jaundice
- 23 Various liver conditions in relation to gall-bladder disease

It is obviously not feasible to cover this ground in a brief paper and therefore only three groups of cases will be discussed the toxemias, the cirrhoses and acute yellow atrophy

I feel it is fair to assume that in biliary tract disease as in other system diseases, disturbances of function precede the development of structural changes. Therefore, it is most important to learn to recognize some of the early signs and symptoms of functional liver disease, and to know the pathways by which the toxic effects created thereby may reach the liver and other vital organs of the body by vicious circle routes, thus preparing the way for organic disease.

In advanced liver disease the differential diagnosis is relatively easy. The history and physical examination coupled with good clinical experience may often alone suggest or actually make the broad major diagnosis. But in early states, and indeed in later stages, of liver disease there is so often a

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935

merging or overlapping of changes in hepato-cellular structure or hepatic damage that one derives much assistance from the laboratory and from duodenal tube studies and from roentgen-ray observations in clarifying the details. Tests for liver function enable us, at least to some extent, to classify better the type of liver disease with which we are dealing.

It is highly important that we learn to recognize the early cirrhosis case by symptoms, signs and laboratory studies before the classical picture has developed and decompensation has occurred. It is certainly no greater diagnostic feat to recognize the terminal picture of either portal or biliary cirrhosis than to recognize the terminal picture of decompensated renal disease as described by Richard Bright over a hundred years ago. The nephritic with marked anemia, edema or general anasarca, cardiac malfunction with chronic passive congestion of liver and other organs, a urine boiling solid with albumin and loaded with granular and waxy casts presents a striking clinical picture. The case with advanced decompensated cirrhosis is likewise easily recognized by his hepatic facies, his pinched sunken features, his sallow color or actual jaundice, his emaciated costal cage, his broom stick arms, his usually greatly enlarged abdomen, distended by ascites, his spindle legs, or in later stages with cardiorenal decompensation, his ankle, leg and scrotal edema, his distended abdominal collateral veins, perhaps a true *caput medusae*, his hemorrhoids and frequently his esophageal varices, his enlarged or shrunken liver. Such marked physical signs constitute an easily identified picture, but this picture is a terminal one.

The time to recognize and to treat cirrhosis of the liver is in the early or latent or compensated stage so that the terminal decompensated stage with ascites may be prevented or become less frequent. I now have a number of such cases recognized clinically and proved by biopsy at exploratory laparotomy, whose disease has been controlled for 10 to 15 years and for whom paracentesis, the ammonia salts and the mercurials, novasurol and salyrgan have not been required. All patients with potential or early known liver disease should select a diet high in carbohydrates, drink no alcohol, guard against a thyrotoxicosis, and against respiratory and enteric disease, and lead an outdoor life. In addition, courses of biliary drainage of the liver for detoxifying purposes and a safe biliary secretagogue, such as decholin should be used. They should be particularly warned against the use of the arsenicals (arsphenamine, neoarsphenamine, even cacodylate of soda) and the quinoline derivatives (atophan, cinchophen, farastan and the like). If such a patient has to undergo operation chloroform as an anesthetic should never be used.

The early symptoms and signs of potential cirrhosis of the liver are similar to those which also occur in the hepatic-intestinal toxemias and in mild hepatitis (the latter less common in America than in tropical zones, where it eventuates in the so-called tropical liver). In all of these conditions there may be an antecedent history of simple catarrhal jaundice, of typhoid or other enteric fever, of constipation from childhood up, perhaps

a statement that calomel courses, or saline purges have been used for years, finally creating and completing the constipation-laxative-enema habit vicious circle. Perhaps an antecedent history may be obtained of the use of the aisenicals, the quinolines, of excess iron or copper, or of a preceding chloroform anesthesia.

These are factors which prepare the way for subsequent structural change. In my opinion the two most important, and perhaps least studied, functions of the liver are its detoxifying power, for instance its ability to deaminize the poisonous amino acids, and its bacteriolytic or bactericidal power, that is its ability to entirely destroy or at least kill the bacteria brought to the liver by the blood, especially the mesenteric-splenic-portal blood.

In the early stages of a potential cirrhosis the patient complains of undue fatigability, a sense of torpor or lethargy. He is unrefreshed after more than eight hours' sleep, which may be heavy but is often broken by disturbed dream states, or even by severe nightmares. Frequently—if one questions—mild to severe cramps in toe, foot arch or leg muscles will be complained of. Diurnal drowsiness, particularly after meals, is common. Patients say that they feel "toxic" or doped. They lose alertness, state that they cannot concentrate, that they feel mentally confused and are increasingly forgetful. Some speak of momentary dizziness, of dancing scotomata or *muscae volitantes*, and some give a history of biliary migraine and vomiting. They may be emotional or tearful, or they may be pessimistic, gloomy, depressed, or even may develop severe melancholia. They are petulant over their appearance, complaining of their sallow color and frequently of acne vulgaris. One will note that the blonds become increasingly sallow, the brunettes increasingly swarthy. The sclerae are icteric, the stools slightly deficient in bile, the urobilinogen index is high, indican may be in excess, liver spots or cloasmata may appear, sometimes petechiae or "ruby points" may come and go. Telangiectases, even the small spider web type, above the costal margins are important signs to note. The differential values of the Van den Bergh test are often helpful. The icterus index may show latent if not actual jaundice. There may be an increase in uric acid, undestroyed by the liver, a diminution of urea, insufficiently formed by the liver, possibly an increase of blood cholesterol. These are all helpful when present but are frequently absent. Bromsulphalein retention, when present, and evidence of diminished liver secretion and excretion of bile as determined by duodenal tube study are of diagnostic value. A positive galactose test suggests hepato-cellular damage but is usually negative in the early stage with which we are now concerned.

It is a question how patients, presenting the above described clinical features, should be classified. In earlier publications, for want of better terms, I have designated them as hepatic toxemias, intestinal toxemias and, when overlapping symptoms were present, as hepatic-intestinal toxemias.

Certainly such symptoms and signs are often the prelude to the appear-

ance of more striking clinical pictures of toxemia or hepatitis, or of cirrhosis itself. The part played in the later evolution of the disease by such factors as disease of the gall-bladder, the heart, the pancreas or the colon must be passed over in this brief summary as must also the existence and importance of certain vicious circles which I have described elsewhere.¹

Now let us turn to a very brief discussion of the classification of the cirrhoses. One may follow either Chauffard's classification which outlines the methods by which cirrhosis is induced, or one of the classifications based upon purely anatomical considerations, such as Adam's or Senator's. However, I prefer Rolleston's classification with its simple division into two main groups. This seems preferable to an etiologic classification, since the causes of cirrhosis are legion, or to a classification based on size, hypertrophic and atrophic, or to an attempt to classify by the relative involvement of the liver and spleen, such as is implied in the terms hepatomegalic, splenomegalic or hypersplenomegalic biliary cirrhosis, etc. Rolleston's classification appeals by its simplicity and by its quick approach to the more common clinical features. He divides the cirrhoses into

- 1 *Ordinary or common cirrhosis*. Elsewhere this is variously described as portal cirrhosis, Laennec's cirrhosis, multilobular cirrhosis, alcoholic cirrhosis and even chronic interstitial hepatitis. In this form, hematemesis is an early symptom, ascites a terminal incident. Jaundice is not prominent. The liver may be either large or small but is multilobularly involved. The spleen is at times enlarged but not so constantly as in group two.
- 2 *Biliary cirrhosis*. Here jaundice is prominent and long continued. Hematemesis and ascites are both less common, although ascites in small amounts may occur just before death. The liver is always enlarged, often extremely so, reaching a weight of 4500 to 6000 grams. The surface is smooth and unilobular. The spleen is usually enlarged, often greatly so. This group Rolleston subdivides into (a) a simple hypertrophic biliary cirrhosis, and (b) obstructive biliary cirrhosis (for instance common duct gall stone).

There are further variations and enlargements of the above two main groups depending on associated lesions such as carcinoma, syphilis, malaria, various cysts, various abscesses, chronic passive congestion from a failing heart, hemolytic jaundice with splenomegaly and so on, all of which add distinctive features and signs which need not be discussed at this time. There are also rarer forms of cirrhosis which must be classed separately: the pigmented cirrhosis with anthracosis (miner's disease), cirrhosis with hemochromatosis—so-called bronzed diabetes with glycosuria, and that rare and obscure cirrhosis described by Kinnear-Wilson with neurological signs pointing to involvement of the lenticular nucleus in the brain.

I apologize for merely outlining this important subject so that there may be space to devote to a very brief word picture of acute yellow atrophy of the liver or, more properly called, acute necrosis. This is a dreadful malady. It is characterized by decreasing size of the liver, by jaundice, fever, by certain nervous symptoms and too frequently by a fatal termina-

tion Some cases called subacute yellow atrophy differ only by the degree and not by the character of the illness and may recover with appropriate treatment, as did a case we recently reported² As particularly dangerous causative factors may be mentioned chloroform narcosis, phosphorus poisoning, the arsenical and quinoline derivatives, carbon tetrachloride, and exposure to the fumes of trinitrotoluene (T N T) and tetrachlorethane As in other liver diseases the ground has been prepared or the patient possesses an individual susceptibility to either the disease itself or to some agent which causes it For instance, a fatal case which I saw recently in consultation during the third stage could be traced back to 17 tablets of cinchophen taken for "arthritis" The arthritis may have helped to prepare the ground and the patient's idiosyncrasy to cinchophen did the rest

The onset is usually insidious because of a latent period of two to four weeks Indefinite malaise, early, mild digestive symptoms or a jaundice at first undistinguished from the simple catarrhal variety may be the initial symptoms There may be vomiting, muscular pains, constipation with bile deficient stools, and bilirubinuria These features characterize the first stage

The onset of the second stage is a turn for the worse with the appearance of nervous symptoms Headache becomes more intense, photophobia, dullness, restlessness and delirium Muscular twitchings extend from isolated muscle groups into general convulsions Babinski's sign is present If one excepts the jaundice the clinical picture resembles meningitis

In the third stage vomiting becomes more troublesome, and may be bloody, the pupils dilate, the pulse is rapid and thready, respirations increase, the temperature may be subnormal or rapidly rise to high fever levels, frequently petechiae and submucous hemorrhages occur, drowsiness becomes progressive, the patient lapses into coma and usually dies

The liver may at first be swollen but rather quickly shrinks and shrinks so that but little percussion dullness may remain The jaundice may increase but never becomes of the obstructive type, the urobilinogen index rising to higher levels The stools are light colored but not clay white The urine appears like strong tea The blood coagulates slowly and contains excess bilirubin, its cholesterol content may vary but is usually decreased, amino acids, leucine and tyrosine, are in excess both in the blood and urine Urea is diminished, uric acid is increased Positive blood cultures are rare, even for *B coli* Blood sugar decreases to dangerously low levels and this decrease parallels the clinical severity of the disease Bromsulphalein dye is retained in the blood The Van den Bergh test yields a biphasic or a delayed direct reaction The galactose test may be positive up to a urine content of six or more grams

Aside from the above details the diagnosis can be suspected because of the jaundice with severe constitutional and cerebral symptoms and particularly because of the decreasing size of the liver

All patients should be given the benefit of urgent treatment, since some

cover, and more will do so by proper treatment. This consists of warmth of the liver region, blood transfusions, intravenous sugar, carbohydrate fluids by mouth, salt and sugar by bowel and subcutaneously, duodenal drainage to remove toxins and general supportive measures. Bile salt preparations by mouth or vein are dangerous until after jaundice has subsided. If one must be tried, decholin is the safest. Sometimes calcium by vein and butyric acid and parathormone may help.

BIBLIOGRAPHY

- LYON, B. B. V., and SWALM, W. A. The therapeutic value of non-surgical drainage of the biliary tract, *Jr. Am. Med. Assoc.*, 1925, **lxv**, 1541-1548.
- LYON, B. B. V., SWALM, W. A., BARTLE, H. J., and STERNER, R. F. Therapeutic effectiveness of dehydrocholic acid in liver and biliary tract disease, *Med. Rec.*, 1934, **cxxv**, 123-128.

TREATMENT OF PERIPHERAL VASCULAR DISEASE BY MEANS OF SUCTION AND PRESSURE *

By E M LANDIS, F A C P , and I H HITZROT, *Philadelphia, Pennsylvania*

AT the meeting of the College in 1934, one of us presented certain observations¹ indicating that blood flow to the extremities could be increased at least temporarily by applying alternate negative and positive pressure. In patients with peripheral vascular disease and advanced organic arterial occlusion this procedure elevated skin temperature conspicuously, often relieved cyanosis, usually diminished rest pain and favored the healing of indolent ulcers. While symptoms were quite generally relieved it was then felt impossible to do more than speculate upon the permanence of that improvement. To quote the statement then made, "The practical importance of suction and pressure in the treatment of peripheral vascular disease will necessarily depend to a great extent on the degree to which collateral vessels take over the function of those arteries which are closed by disease. Sufficient time has not elapsed to justify any conclusions concerning the real clinical usefulness of the procedure."

It is the purpose of the present report to present a summary of our experience in the first 75 cases subjected to suction and pressure therapy (table 1). An attempt will be made to give a fair cross-section of general

TABLE I
Summary of 75 Consecutive Cases Treated by Means of Suction and Pressure

Diagnosis	Number	Age—Years			Suction and Pressure Therapy—Hours		
		Average	Highest	Lowest	Average	Highest	Lowest
Arteriosclerosis, senile	23	69	80	52	22	91	2
Thromboangitis obliterans	22	41	61	26	31	119	5
Diabetes, arterio sclerosis	30	62	78	42	26	90	2
Total	75						

Note. Treatment for two to five hours represents merely attempted palliation in patients in whom conservative therapy was essentially hopeless.

* Read at the Philadelphia meeting of the American College of Physicians, May 3, 1935. From the Robinette Foundation, University of Pennsylvania Hospital, and the Metabolic Division of the Philadelphia General Hospital. Aided by grants from the Philadelphia Heart Association and from the Committee on Scientific Research of the American Medical Association.

results in hospital cases and out-patients, including, without omission, all cases so far treated even briefly by this method

The apparatus used was the same as that described previously^{2,3} During treatment the patients sat or reclined in bed. The affected extremity was inserted into an aluminium chamber and lay in the horizontal plane upon a pillow in the bottom of the chamber. The thigh, protected when necessary by a layer of gauze bandage, was encircled at a point approximately six inches above the knee by a rubber cuff with two leaves, one sealing during pressure, the other sealing during suction. A layer of adhesive tape was applied to each cuff to keep the rubber in close contact with the skin. Suction amounting to between 80 and 120 mm of Hg was applied for 25 seconds alternately with positive pressure of 40 to 80 mm of Hg for 5 seconds. The time required to change the air pressure within the aluminium chamber from -120 to $+80$ mm of Hg was reduced to about 3 seconds in order that the negative pressure might be applied as efficiently as possible. Until patients became familiar with the apparatus it was usually expedient to use -80 and $+60$ mm of Hg for 25 and 5 seconds, respectively, increasing to -120 and $+80$ mm of Hg unless large changes of pressure were contraindicated.

In general when rest pain was severe, or when ulcers had not yet begun to heal, the affected extremities were exposed to suction and pressure for one or two hours twice daily. After rest pain had diminished somewhat and after ulcers had begun to heal, the duration of treatment was reduced to one or two hours at first once daily, then three times weekly and finally to one or two hours once weekly. Out-patients with relatively mild symptoms were treated for periods of one or two hours three times weekly or less.

Ulcers were dressed daily with vaseline gauze, antiseptics were used only rarely, since even the mildest seemed to delay the growth of granulation tissue and epithelium in ischemic extremities. Parts involved in dry gangrene were merely covered with sterile gauze.

A few of the patients had previously received citrate solution or typhoid vaccine intravenously without relief. Most of the ward patients had been treated by other conservative means, including particularly the thermo-regulated cradle and vasodilator drugs, before suction and pressure were resorted to on account of persisting symptoms. In these cases the thermo-regulated cradle was used during the intervals between suction and pressure treatments. Out-patients received the usual advice concerning care of the extremities and smoking. They were advised to use hot sitz baths and in selected instances salt solution by mouth was prescribed.

The extent of organic occlusion and the development of collateral circulation were tested at intervals by measuring skin temperature while the forearms were heated, either by means of warm water or electric pads.

The 75 cases considered in this report include 23 with arteriosclerosis, 22 with thromboangitis obliterans and 30 with diabetes and arteriosclerosis. The average age of the arteriosclerotic group was 69 years, ranging from

80 to 52 The ages of the diabetic patients averaged 62 years, while the patients with thromboangitis obliterans were approximately 20 years younger, averaging 41 years

Owing to limited facilities it was possible only to assist in recovery from the more advanced manifestations of ischemia,—severe rest pain, indolent ulceration or marked intermittent claudication No attempt could be made to continue suction and pressure therapy as a prophylactic measure in order to avoid recurrences or to avert future difficulties The average amount of treatment ranged from 22 to 31 hours with several instances of 90 hours or more Treatment totalling only a few hours (such as two or five hours) represents attempted palliation in patients in whom any conservative therapy was essentially hopeless from the outset It was our purpose, however, to observe the effects of suction and pressure on peripheral vascular disease of all grades of severity, including even the most hopeless cases

The general results are shown in table 2 in which the effects have been tabulated under the headings good, fair and poor A good result includes

TABLE II
General Results of Suction and Pressure Therapy

Result	Number of Cases	Per Cent
Good	38	51
Fair	10	13
Poor	27	36
Total	75	

Analysis of Cases Designated "Poor"

Too far advanced or sloughs	Massive gangrene	6		
Infection		4		
Drifted away		5		
Incomplete		12		
Total		27		
			<i>Amputations</i>	10

obliteration of rest pain, distinct lessening of claudication and the complete healing of ulcers previously increasing or indolent under other conservative measures Such outstanding relief, which could in all fairness be attributed to suction and pressure therapy, was observed in 51 per cent of the 75 cases A fair result includes almost, but not quite, complete relief of rest pain, slight but definite lessening of claudication, and healing of lesions except for very small sinuses or minute areas There was no evidence of advance in symptoms or signs, the tendency being toward very slow improvement in this group which comprises 13 per cent of the total

The designation "poor" has been used to indicate that the relief of symptoms ordinarily observed *immediately during* suction and pressure therapy has not been accompanied by significant relief of symptoms *between*

treatments It is possible that prolonged and frequent therapy might accomplish more than the limited amount we have been able to use in these cases This group includes six patients who had massive gangrene or deep sloughs, in the face of which suction and pressure therapy was useless except as a temporary palliative measure Four patients had, or developed, advancing infection These 10 cases required amputation eventually Five cases listed as poor results drifted away, three of these in spite of definite improvement, two because of dissatisfaction with the results obtained The remaining 12 patients are still under treatment which is incomplete and has not progressed far enough to permit estimation of eventual results Six of these 12 patients, however, are showing encouraging progress at the present time

It may be concluded that "good" and "fair" results were obtained in 64 per cent, any error being, we believe, in the direction of too low a figure Similarly the estimate of poor results in 36 per cent is probably too high since it includes certain cases which we would now regard as hopeless from the outset, and a certain number in which therapy has not had a fair trial

When the results of suction and pressure therapy are arranged according to diagnosis (table 3) it becomes evident that the poorest results have been

TABLE III
Results of Suction and Pressure Therapy According to Diagnosis

Diagnosis	Result			Total
	Good	Fair	Poor	
Arteriosclerosis	12	3	8	23
Thromboangitis obliterans	52%	13%	35%	22
	14	1	7	
Diabetes	64%	5%	31%	30
	12	6	12	
	40%	20%	40%	

obtained in diabetes, with slightly better results in simple arteriosclerosis The highest percentage of good results was obtained in thromboangitis obliterans This distribution agrees in general with observations on other types of conservative therapy

Landis and Hitzrot⁴ published, in March 1935, a summary of the results observed in 30 cases treated up to July 1934 (table 4) A "good or fair" result was obtained in 24 cases Most of these patients were hospitalized and had been treated conservatively by the usual methods without success prior to the use of suction and pressure therapy The apparent benefit derived in these 24 patients seemed therefore more significant than it would have been if unselected cases had been treated It has been possible to obtain follow-up data on 23 of these 24 cases Thirteen had no further symptoms of peripheral vascular disease during 6 to 22 months after discharge,

TABLE IV

Persistence of Improvement Once Obtained

Of 30 severe cases (Landis and Hitzrot,⁴ treated prior to July 1934 and reported March 1935)

6 Poor
24 Good and fair

Of the 24

13—No further symptoms in 6 to 22 mos (average 11 mos)

1—Mild recurrence, yielding to treatment

6—Died, ages 78, 62, 57, 55, 75, 46

1—Cerebral hemorrhage

3—Pneumonia

2—Coronary occlusion

3—Relapses

2—Amputation of leg

1—Amputation of toe

1—Lost

Total 24

the average period being 11 months. One case presented a mild recurrence yielding easily to suction and pressure therapy. Six patients died, one of cerebral hemorrhage, three of pneumonia, and two of coronary occlusion. The causes of death alone indicate the precarious general condition of most patients with advanced peripheral vascular disease. Definite relapses were observed in three instances after suction and pressure therapy had healed indolent and painful lesions. In the first patient a necrotic lesion of the great toe appeared six months after discharge and advanced slowly in spite of suction and pressure therapy. Amputation of the leg above the knee revealed marked sclerosis of the femoral artery. A second case appeared four months after discharge with gangrene of a toe in which ascending infection contraindicated the use of suction and pressure, leading finally to amputation above the knee. The third case suffered from subacute thromboangitis obliterans which had already required amputation of three digits in the course of two years. Suction and pressure had been required to heal the ulcer remaining after the last amputation. One year later the patient reappeared with a deep ulcer at the base of another digit. Involvement of an interphalangeal joint and osteomyelitis of a phalanx contraindicated suction and pressure therapy. The fifth toe was amputated in January 1935, local heat, vasodilator drugs and suction and pressure being used to aid healing of the wound. Whether or not continued treatment of these three patients after discharge from the hospital would have modified the final result is not known. These relapses suggest, however, the need for continuous after-treatment even though ulcers have healed and rest pain has disappeared.

A number of other patients not shown in this table have been followed over briefer periods of time after suction and pressure therapy has been stopped. If these are included, the follow-up data indicate continued relief in at least 26 patients of the group from one month to two years after discontinuance of suction and pressure therapy.

An analysis of possible causes of relapse in 6 of the 48 cases discharged with good or fair result is of considerable interest (table 5) Discharge from the hospital with an imperfectly drained lesion was followed by a

TABLE V

Causes of Relapse—6 Cases in 48 with Fair or Good Result

A	Discharged with imperfectly drained lesion	1
	2 mos—healed with renewed treatment	
B	Advancing subacute thromboangitis obliterans	2
	(a) 1 year—gangrene of toe amputation of toe	
	(b) 6 weeks—return of rest pain	
C	Widespread advanced arteriosclerosis	3
	(a) 6 mos—ulcer healed with renewed treatment	
	(b) 4 mos—gangrene toe, mid-thigh amputation, sclerosed femoral artery	
	(c) 6 mos—gangrene toe and infection, mid-thigh amputation	

relapse with increased rest pain and increased ulceration at the end of two months This ulcer was healed with difficulty by renewed treatment In acute or subacute thromboangitis, recurrence or relapses can be expected since the disease ordinarily advances at a rate too rapid to allow the compensatory development of collateral blood flow One patient returned in a year with gangrene of a toe requiring amputation Another with severe rest pain returned after six weeks with renewed rest pain, the first period of treatment having been quite definitely insufficient

Widespread advanced arteriosclerosis involving the femoral artery seemed to be responsible for at least three recurrences at four to six months after cessation of treatment In one patient renewed treatment was successful in healing the lesion In two patients previously mentioned, mid-thigh amputation was necessary, one on account of advancing gangrene and the other on account of acute infection

As might be expected from the advanced age of at least two-thirds of these patients the death rate in a group followed over two and a half years is relatively high (table 6) Eleven of the 75 cases treated with suction and pressure therapy have died, three of coronary occlusion, one of cerebral hemorrhage, four after amputation and three from pneumonia The lower

TABLE VI

Deaths—11 of 75 Cases

1	Coronary occlusion	3
2	Cerebral hemorrhage after prostatic punch operation	1
3	Post-amputation	4
4	Pneumonia	3

Possible Injurious Effects of Suction and Pressure Therapy

1	Amputation hurried	3
	In 2 amputation inevitable before suction-pressure therapy	
	In 1 amputation being seriously considered	
	In all 3 suction-pressure therapy used to exhaust all possible conservative measures	
2	Thrombosis or embolus	none
3	Petechiae	2
	Both diabetics no sequelae	

portion of the table presents possible injurious effects of suction and pressure therapy. In two of these cases amputation was inevitable before suction and pressure were applied, the procedure being tried only to exhaust the use of all possible conservative measures. In the third case amputation was hastened owing to the development of ascending infection. In this instance amputation was being seriously considered as the only alternative before suction and pressure therapy was started as a last resort. We have observed no instances of massive thrombosis or embolism. A few cases have become progressively worse during suction and pressure therapy, owing to the presence of massive gangrene or deeply penetrating sloughs. Though the area of gangrene slowly increased in size there was no massive increase in ischemia, and there were no symptoms or signs that could be ascribed to a large thrombus or embolus. Petechiae appeared in two diabetics with delicate skin without sequelae in either instance. Improper adjustment of the cuff above the thigh makes hemorrhages more likely to appear since constriction prevents complete evacuation of blood during the period of pressure. This complication can be avoided by adjusting the cuff carefully and by observing the emptying of the vessels during pressure.

TABLE VII

Factors Predisposing to Failure or Very Slow Improvement in 12 Cases ("Poor Result")

Extreme arterial occlusion	8
Massive gangrene or slough	8
Badly infected lesions	5
Osteomyelitis	3
Severe dermatophytosis	2

It is essential to know what conditions are most apt to lead to failure of conservative therapy including suction and pressure (table 7). In 12 cases classified under "poor results" suction and pressure therapy, after fair trial, failed to arrest the effects of ischemia. Extreme arterial occlusion involving the large vessels was present in eight cases. Deeply extending gangrene or massive sloughs were present in eight cases. In these patients the immediate problem is primarily mechanical since devitalized tissue must be removed before healing can take place. Infection and pain are both apt to increase as long as necrotic tissue remains. Judicious surgery plus suction and pressure therapy should yield better results than either procedure alone.

Infection appeared to be extending in five cases. Acute ulcers are more dangerous to treat by suction and pressure than are chronic ulcers which are well walled off by inflammatory tissue. While patients with open lesions are being treated it is essential to investigate the extremity before each treatment in order to be certain that there is no phlebitis and that infection is not spreading. Patients with even slight elevation of temperature should be treated only with the utmost caution. If the presence of encapsulated pus is suspected suction and pressure therapy should not be used. When

such lesions are present external drainage must be complete and continuous. It is this possibility of harm from spreading infection that makes suction and pressure therapy distinctly not a routine procedure. On the contrary, it can be decidedly dangerous under some circumstances. Patients who are undergoing suction and pressure therapy must be followed carefully by a physician,—they cannot be left to the attention of technicians alone.

Osteomyelitis was present in three cases. As might be expected cutaneous lesions healed satisfactorily, but as long as drainage from the infected bone continued sinuses remained. These sinuses could not be closed by suction and pressure therapy. Osteomyelitis was responsible for one amputation after a cutaneous lesion had disappeared, and was responsible for two "fair" results in which sinuses remained after the cutaneous lesions and the symptoms had largely disappeared. Severe dermatophytosis in conjunction with advanced organic occlusion was, we believe, responsible for two failures. It is our impression that the application of potassium permanganate even in weak solution may affect the ischemic skin deleteriously. Dermatophytosis in conjunction with very mild organic occlusion is of little consequence, but when combined with severe organic occlusion it becomes a major complication.

Fourteen cases have been studied with respect to the change in skin temperature of the lower extremities when the forearms were heated either by immersion in warm water⁵ or by electric pads. In seven (table 8) of these

TABLE VIII
Increase in Vasodilator Response Following Suction and Pressure Therapy

Patient	Diagnosis	Treatment Hours	Vasodilator Response		Time Elapsed	Therapeutic Result
			Before	After		
1 Po	T A O	71	°C	°C		
2 He	T A O	24	None	29.2	22 mos	Good
3 Ro	T A O	112	None	30.2	19 mos	Good
4 Ca	T A O	112	27.6	30.6	22 mos	Fair (claud)
5 Ha	T A O	20	28.0	29.5	6 mos	Fair (osteo)
6 Li	Arterioscl	91	None	26.3	11 mos	Good (sl pain)
7 Fi	Diabetes	70	None	29.5	6 mos	Good
	Arterioscl	16	None	27.4	2 mos	Good

14 cases a "good" or "fair" therapeutic result has been accompanied by definite objective evidence of improvement in collateral blood flow as measured by increase in vasodilator response. Over a period of 19 to 22 months the vasodilator response may improve remarkably, indicating that it is well worth while to temporize in crises of pain or claudication in order that time may be gained for the development of adequate collateral circulation. As this table shows, improvement in circulation may be very conspicuous by objective test.

An equally large number of patients (table 9), however, showed no measurable change in their vasodilator response after periods of two months to one year. These patients have, however, been followed over briefer periods of time and objective signs of collateral circulation may eventually develop. The relief of symptoms in this group was, in general, not as good

TABLE IX
No Change in Vasodilator Response Following Suction and Pressure Therapy

Patient	Diagnosis	Treatment Hours	Vasodilator Response		Time Elapsed	Therapeutic Result
			Before	After		
8 Sa	Arterioscl	14	°C 23.4	°C 24.4	3 mos	Moderate relief claud
9 Ba	Arterioscl	20	26.8	23.4	2 mos	Rest pain abolished. Claud delayed
10 F ₁	Arterioscl	14	29.5	29.5	2 mos	Rest pain moderately relieved. Claud unchanged
11 Ec	Arterioscl	17	None	None	2 mos	Ulcer healed, rest pain relieved
12 Ra	T A O	22	None	None	2 mos	Rest pain diminished 75%
13 Dr	T A O	60	None	None	1 yr	Rest pain partly relieved, ulcer healed
14 Tr	Diabetes	44	None	None	6 mos	Relapse, gangrene, amputation

as in the other group who showed conspicuous increase in vasodilator response. One patient returned after six months with a relapse requiring amputation. Conservative therapy was justified, however, because of the symptomatic relief afforded each patient at least temporarily.

In summary, suction and pressure therapy has been used in the treatment of 75 patients with peripheral vascular disease. Negative pressures between -80 and -120 mm Hg and positive pressures between +40 and +80 mm Hg were applied alternately for 25 and 5 seconds, respectively, beginning usually with the lower pressures. Patients were treated for one to two hours at first once or twice daily, then three times weekly and finally, as the symptoms and signs diminished, once weekly.

Cyanosis was usually diminished, symptomatic improvement was sometimes observed, however, without significant change in skin color. The rest pain of ischemia was usually abolished during actual use of suction and pressure and gradually became less severe in the intervals between exposure to pressure variations. Ulcers enlarging or indolent under ordinary conservative treatment usually began to heal soon after suction and pressure therapy was instituted. Intermittent claudication became in general milder and exercise tolerance was slightly, but definitely, increased.

Suction and pressure therapy was of no definite lasting service in patients with osteomyelitis, deeply extending gangrene or large sloughs. A

certain number of patients with severe, widely disseminated arteriosclerosis did not improve

This form of therapy is *contraindicated* in patients with phlebitis, encapsulated pus or acute spreading infection. Patients must be followed day by day so that any change in the clinical picture may be detected. It is only in this way that the possible injurious effects of suction and pressure can be avoided. The therapy should be applied with caution in appropriate cases, under the direct supervision of a physician.

Suction and pressure therapy appears to be a worth while addition to the other conservative methods of treating peripheral vascular disease. Good results can be obtained even when organic obstruction has advanced to the stage in which arterial blood flow can no longer be increased by measures depending on vasodilatation. Symptoms and signs of ischemia have been relieved when other conservative measures proved ineffectual. The method may be of particular service in increasing local blood flow temporarily during episodes of pain or ulceration, so that time is gained for the development of adequate collateral circulation. This development of collateral circulation is slow, but over periods of six to 22 months has been observed to be capable of increasing the vasodilator response in the lower extremities with persisting symptomatic improvement.

REFERENCES

- 1 LANDIS, E M. Observations on the diagnosis and treatment of peripheral vascular disease, *ANN INT MED*, 1934, viii, 282-295
- 2 LANDIS, E M, and GIBBON, J H, JR. Effects of alternate suction and pressure on circulation in the lower extremities, *Proc Soc Exper Biol and Med*, 1933, xxx, 593-595
- 3 LANDIS, E M, and GIBBON, J H, JR. Effects of alternate suction and pressure on blood flow to the lower extremities, *Jr Clin Invest*, 1933, xii, 925-961
- 4 LANDIS, E M, and HITZROT, L H. The clinical value of alternate suction and pressure in the treatment of advanced peripheral vascular disease, *Am Jr Med Sci*, 1935, clxxix, 305-326
- 5 LANDIS, E M, and GIBBON, J H, JR. A simple method of producing vasodilatation in the lower extremities, *Arch Int Med*, 1933, lxi, 785-808

VON GIERKE'S GLYCOGEN DISEASE¹

By LIONEL M LINDSAY, M D , ALAN ROSS, M D , and
F W WIGGLESWORTH, M D , *Montreal,
Quebec, Canada*

SINCE 1929, when von Gierke first reported two cases of the syndrome which now bears his name, a great interest has been shown in this disturbance of glycogen metabolism. Now that attention has been called to the disorder numerous cases have been reported from Europe, Australia and America, and a search into medical literature reveals the fact that several undoubted cases were reported under various names prior to 1929.

The disease may be defined as a disturbance of glycogen metabolism which appears in early infancy and is characterized by an abnormal deposit of glycogen in the liver, kidneys, heart and other organs which become so engorged with glycogen that they assume an enormous size. The peculiarity of this stored glycogen is that it becomes in some way fixed and cannot be mobilized to any extent by natural means.

The most striking cases are those in which the liver is chiefly involved. The infant's abdomen is noticed to be unduly large and palpation reveals the fact that the enlargement is due to the enormous size of the liver. There are no other symptoms of disturbed liver function, such as jaundice or ascites, and the Van den Bergh test is negative. The spleen is not enlarged.

The second characteristic of the disease and one dependent on the fixation of glycogen in the liver, is a permanently low blood sugar which may fall to 20 or 30 mg per cent in the fasting state and yet not be accompanied by any symptom of the hypoglycemic syndrome. The sugar tolerance curve is abnormal being slower to rise and more prolonged than normal. Acetonuria may be present especially in the fasting state. The injection of adrenalin fails to produce the usual marked rise in blood sugar but the ketosis may be increased. Some cases show a lipemia and an abnormally high concentration of cholesterol. As might be expected the reaction to insulin is usually severe and accompanied by symptoms of shock.

The etiology of this disease is quite obscure. As regards the pathogenesis little is known. Attention has naturally been concentrated on the factors which govern glycogenesis and glycogenolysis. Normally the liver extracts glucose and other nutrients from the blood and stores them as glycogen. When the blood sugar falls below a certain level a demand is made on the liver for a supply of glucose.

The muscles also participate in the formation of glycogen from glucose. When the muscle contracts glycogen breaks down and lactic acid is formed. The latter is carried by the blood to the liver and there converted into glycogen again.

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935

The exact mechanism by which glycogen is mobilized is not known. It appears to depend on a combination of endocrine and nervous factors. The prime governor of carbohydrate metabolism is probably insulin which not only regulates the formation of glycogen but also the combustion of glucose with resultant reduction of blood sugar. Adrenalin, on the other hand, has the faculty of mobilizing glycogen and causing a sharp rise in blood sugar and blood lactic acid. A similar rise can be produced by stimulation of the splanchnic nerves. Adrenalin probably acts on the glycogen through the medium of the enzyme, amylase, which normally controls the glucose-glycogen balance.

The secretion of the pituitary and thyroid glands is also concerned in the complex mechanism of glycogen metabolism.

In the case of von Gierke's disease the study of amylase in the liver, blood and urine by various observers has not led to uniform results. It would seem that although sufficient amylase is present in the liver and blood it cannot, for some unknown reason, liberate glucose from the glycogen. How glycogen and amylase can be found in the liver without the production of glycogenolysis is a puzzle for which various theoretical solutions have been advanced. An interesting fact which may have some bearing on the question has been observed in postmortem examination. The liver glycogen fails to disappear within a few hours after death, as should normally occur, but may be found for many days afterwards.

One must conclude that either the glycogen is of a different quality, resistant to the action of normal enzymes—or that there is some barrier between the enzymes and the glycogen. At present there is little evidence to support either of these suppositions.

Bichoff, and Putschar¹ were the first to report examples of the *cardio-megalic* form of the disease. The heart in these cases may be five or six times the normal size. The true nature of these cases has rarely been recognized before death. They have usually been considered as cases of idiopathic cardiac hypertrophy or of diffuse rhabdomyomas. The latter have been known for some time to be rich in glycogen.

The symptoms of the cardiac cases are not characteristic. The infant fails to grow and develop normally and is subject to respiratory infections. Occasionally dyspnea, cyanosis and cardiac murmurs are observed. In both cardiac and hepatic forms of the disease the surprising thing is that the function of the affected organ is apparently so little impaired.

It may be only by examining a biopsy section of the liver that the real nature of the condition can be ascertained, indeed, until recently, most cases of von Gierke's disease have been diagnosed only by postmortem examination. By proper staining it is then found that the parenchymal cells of the affected organ are greatly swollen and are engorged with large granules of glycogen.

The disease appears to be familial. Several instances of two or three affected members of a family have been reported. The enlarged liver and



FIG 1 Von Gierke's disease Paul B, aged 2½ years, showing fat cheeks, large abdomen and the lower level of the liver



FIG 2 Contour of body with patient in dorsal decubitus

abdomen are noticed early in infancy and seem to progress to a certain point where they remain stationary for some years. There is evidence that those who survive to adolescence show some improvement. Physical growth is impeded and the term hepatic infantilism has been applied to certain cases.

No known treatment in any way influences the course of the disease. Many cases have died of pneumonia or other intercurrent infections. One case developed diabetes mellitus, a fact which may be of some significance. When one realizes that the nature of the disease has been recognized only for the past six years it is not surprising that so little is known of its ultimate outcome. One may expect that with continued study of suitable cases a more complete understanding not only of this disease but also of the physiology of carbohydrate metabolism will ensue.

The recent studies of van Creveld² in Amsterdam and Rauh and Zelson³ in New York have added much to our knowledge of this disorder. The pathological study recently published by Humphreys and Kato⁴ has also helped to clarify some of the obscure points. These observers have reviewed all cases in the literature and have added three more in which the heart was predominantly involved. They claim that there are but 15 proved cases of glycogen storage disease on record.

The following case illustrates well the hepatic type of von Gierke's disease.

CASE REPORT

Paul B., a French Canadian boy of 27 months, was admitted to the Childrens Memorial Hospital in April 1934. His complaints were enlarged abdomen, and discharging ears.

He was the fifth child in the family, apparently a normal, full term infant weighing 7½ lbs at birth. He was breast fed for five months and was then given a mixed diet with cod liver oil and orange juice. At seven months of age he began to vomit and his abdomen was noticed to be unduly large.

From that time until admitted to the hospital, he had frequent attacks of vomiting and his abdomen continued to enlarge slowly. His appetite was good and the bowels were regular. Three months prior to admission, he was taken acutely ill with fever and convulsions. Soon after both ears began to discharge.

His father and mother were both 36 years of age and apparently healthy. There were five other children, one of whom, a boy, had died of pneumonia at 10 months of age and this child is said to have had a "big stomach like Paul."

Examination on admission showed a rather short boy (figures 1 and 2) giving the impression of being very fat,—because of his fat cheeks and chin, and very large abdomen. There were "pads of fat" over both knees and elbows and also over the distal and middle phalanges of all fingers. In contrast to these evidences of obesity the nutrition of the arms and especially of the legs was poor and the muscles were soft and flabby. His height was 31 inches and his weight 29 lbs. There were no signs of rickets and he had 16 teeth. The skin was pale but not jaundiced. Mentally the patient was very placid and cooperative.

The lungs were negative. Auscultation of the heart revealed a systolic murmur at the apex. The radiogram showed no enlargement, though the heart was pushed up by the enlarged liver.

The abdomen was very large with dilated superficial veins over the upper part. On palpation the liver was found to be enormously large, extending below the umbilicus in the mid-line. Its surface was smooth and firm. The spleen was not palpable. There was no evidence of free fluid in the peritoneal cavity. The genitalia were normal.

Examination of the urine was negative. The Mantoux and Wassermann tests were both negative. The blood showed a mild anemia with a leukocyte count of 11,000.

Rather extensive chemical studies of the blood were made, but only the following abnormalities were found. Hypoglycemia, ranging from 20 to 37 mg per cent, in the fasting state, low sugar tolerance curves, no rise in blood lactic acid after injection of adrenalin, but development of slight acetoneuria, lipemia (0.75 per cent fatty acids) and high cholesterol, 375 mg per cent. Tests with sugars for liver function gave normal figures.

An attempt was made to outline the kidneys by means of uroselectan, but owing to interference from the enlarged liver, satisfactory outlines indicating enlargement were not obtained.

From these clinical and biochemical observations it seemed justifiable to make the diagnosis of von Gierke's glycogen disease of the hepatic type. To corroborate the diagnosis a small section was removed from the liver. Chemical analysis of this revealed three times the normal amount of glycogen and only one-third the amount of fat usually found.

Microscopic sections (figures 3 and 4) stained by the routine (hemalum, erythrosin and saffron) method presented a very characteristic appearance. The liver cells were greatly swollen and instead of taking the cytoplasmic stain, they were tinted a faint yellow by the collagen stain (saffron). This material gives a positive reaction for glycogen both by the Best's carmine and the iodine method. The nuclei appeared normal and were centrally or excentrically situated.

The lumen of the liver sinusoids appeared to be occluded by the pressure of the enlarged parenchymal cells. A few dense elongated nuclei were the only evidence of their presence and as a result the lobules appear bloodless. Under very low power the liver presented a well lobulated appearance obviously due to an early cirrhosis of the portal type. Higher magnification showed a mild lymphocytic and polymorphonuclear infiltration of the portal spaces. Here and there could be seen one or two glycogen-laden liver cells cut off from the rest of the lobule by fibrosis.

This increase of fibrous tissue has been noted by others in connection with glycogen disease. In the light of our present knowledge our pathologist reexamined the liver of a case of portal cirrhosis in an infant who had died 9 months previously and he found the typically enlarged liver cells filled with glycogen. From this it would seem that whatever may be the cause of glycogen disease, it tends to produce cirrhotic changes in the liver.

Now after observing the boy for just a year, we find very little change in his condition. The liver is possibly a little larger. The blood sugar curve is essentially the same. He has apparently grown only one-half inch in height and his weight is still about 30 lbs. He eats and sleeps well, feeds himself in a most deliberate fashion and has a definite penchant for potatoes and bread. He is exceptionally unemotional, rarely laughs or cries, his expression is stolid, but not stupid. He talks little but can understand both French and English. He is unable to walk without assistance, but can push a small chair about the ward.*

* Within a few days of the presentation of this report, the patient died of a rapidly progressive pneumonia. At autopsy the liver was found to weigh 2150 grams, which is about four times the normal weight at his age. The spleen was slightly enlarged. The heart, kidneys and endocrine glands were not grossly affected. The complete pathologic study will be published at a later date.



FIG 3 Section of liver showing swollen parenchymal cells and early cirrhosis in the portal spaces. Alcohol fixed. Hemalum, erythrosin and saffron stain. $\times 60$

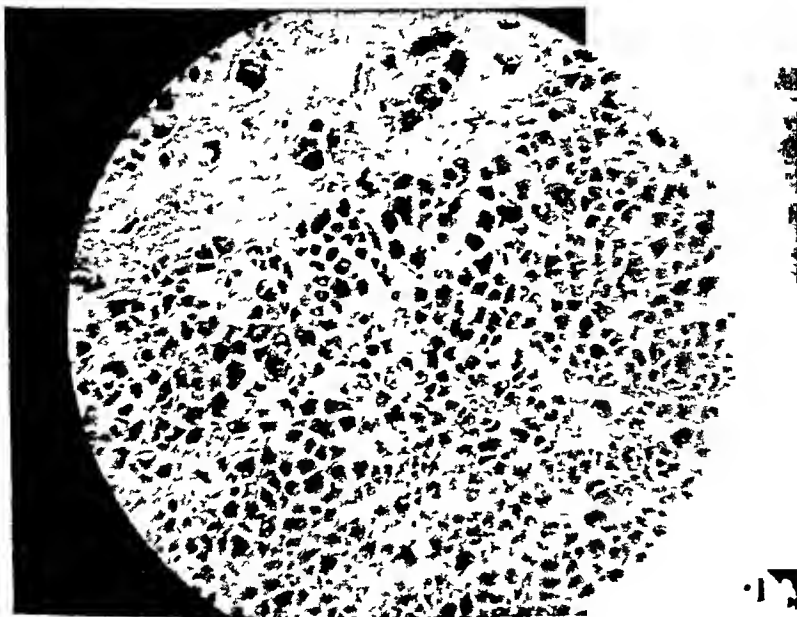


FIG 4 Liver stained by Best's carmine method. Marked retraction of cells due to alcohol. Note the liver cells in the portal space at the top of the picture. These have been cut off from the rest of the lobule by the cirrhotic process. $\times 100$

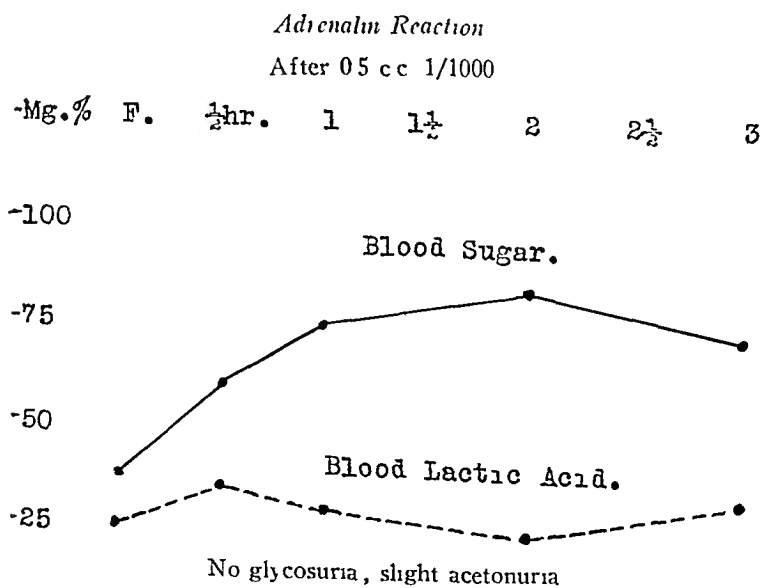
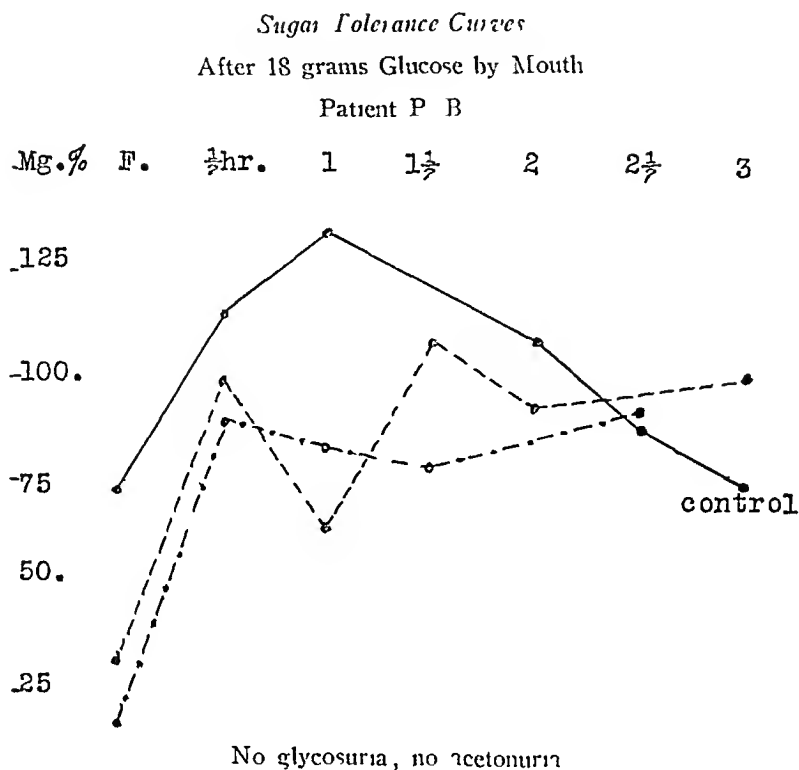


FIG 5

REFERENCES

- 1 BISCHOFF, G Zum klinischen Bild der Glykogen-Speicherkrankheit, Ztschr f Kinderheilk, 1932, 111, 722-726
- PUTSCHAR, W Über angeborene Glykogenspeicherkrankheit der Herzens, Beitr z path Anat u z allg Path, 1932, 26, 222-232
- 2 VAN CREVELD, S Investigations on glycogen disease, Arch Dis Child, 1934, 1, 9-26
- 3 RAUH, L, and ZELSON, C Disturbance in glycogen metabolism with hepatomegaly, Am Jr Dis Child, 1934, 111, 808-820
- 4 HUMPHREYS, E M, and KATO, K Glycogen storage disease, Am Jr Path, 1934, 1, 589-614

DIVERTICULOSIS OF THE LARGE INTESTINE; AN EVALUATION OF HISTORICAL AND PERSONAL OBSERVATIONS

By HAROLD C OCHSNER, M D, *Waukegan, Illinois*, and J ARNOLD BARGEN, M D, F A C P, *Rochester, Minnesota*

THE nature and incidence of diverticula of the large intestine have offered a fertile field for study and speculation for several centuries

Littre, in 1700, mentioned "diverticular hernia" without explaining it Fischer has said that, although the first description of diverticula of the intestine is usually attributed to Sommering in his translation into German of Matthew Baillie's "Morbid Anatomy," in 1794, Voigtel cited previous cases which had been recorded by Schroch, Riolan, Gunz, Morgagni and Haller

The subject of diverticula of the intestine was discussed by Cruveilhier in 1849 W J Mayo, Wilson, and Giffin, in 1907, were the first to record a group of cases in which actual demonstration of the pathologic changes, which occurred in diverticulitis, was established during life In the same year, Moynihan called attention to the mimicry of carcinoma by diverticulitis In 1909, Giffin and Wilson described the occurrence of peridiverticulitis, and in 1911, Wilson described in detail the pathology, pathogenesis, and complications of diverticulitis In 1912, Giffin reviewed the clinical aspects of 27 cases of diverticulitis of the large intestine, in which operation had been performed at The Mayo Clinic from 1902 to 1912

The first preoperative roentgenologic demonstration of diverticulitis is attributed to LeWald, the surgical aspects of this case were reported by Abbe in 1914 Comprehensive studies were reported by Rankin and Brown The former observers noted an incidence of 5.67 per cent in 24,620 roentgenologic examinations of the colon W J Mayo reported an incidence of 5.71 per cent in 31,838 examinations in the period from 1924 to 1930

Erdmann expressed the opinion that the presence of diverticula in the intestine merits no greater attention than does that of the appendix or gall-bladder Bell⁴ said that the condition of multiple diverticula, so-called diverticulosis, is perhaps chiefly of academic interest Case described diverticulosis as a symptomless condition which commonly was encountered during roentgenologic examination of the alimentary tract W J Mayo said that his observation that diverticulitis developed in 12 per cent of cases of diverticulosis was probably an overestimate, but Rankin and Brown discovered that this transition occurred in 17 per cent of their cases Although diverticulosis itself is essentially an innocuous lesion, it appears to suggest a potential danger which should not be overlooked

* Submitted for publication February 5, 1935
From The Mayo Clinic, Rochester, Minnesota

W J Mayo expressed the opinion that neither obesity nor constipation is a real cause of diverticulosis, and that muscular weakness of the colon is probably the underlying factor. Telling, who was one of the earliest observers, felt that deficiency of the muscularis was a factor. Lockhart-Mummery and Hodgson said that, among certain individuals who are past 45 years of age, there is a tendency for the muscle sheath to lose its tone, and that the earliest stage of diverticulosis is the formation of pulsion diverticula, which results from weakness of the musculature. Whether this weakness is congenital, acquired, or both, has not been determined, although many observers, especially E T Bell, believe that it is congenital in origin. The relationship of the blood supply to the development of diverticula is problematic. Graser's observation of the etiologic relation of venous stasis and enlargement of the foramina through which the vessels pass has not been confirmed.

It is a short step from the formation of diverticula to the production of an actual diverticulitis. Beer described the process as a formation of fecal masses in the diverticula, with pressure atrophy of the mucous membrane, and eventually ulceration and secondary infection. If, with edema of the walls, there results a closure of the orifices leading into the bowel proper, the stage is perfectly set. The explanation is so attractive that it seems remarkable that changes, which are the result of inflammation, do not occur more frequently in diverticula.

PERSONAL OBSERVATIONS

Because a large number of patients, who have centered their symptoms about the intestine, present themselves for examination at the clinic in any given period, an unusual opportunity for investigation of this problem seemed at hand. The many conflicting opinions about the nature, incidence, and symptoms of diverticulitis and diverticulosis seemed to justify a statistical study of the cases which had been observed at the clinic in one year.

The relatively low incidence of diverticulosis of the colon is suggested by the fact that this condition was discovered to affect only 0.4 per cent of the patients who registered at the clinic in the selected year. This percentage is undoubtedly too low, as is indicated by the discovery of diverticula in 6.9 per cent of 447 cases which came to necropsy in the same period, in the majority of these cases the condition was not recognized during the clinical examination because the patients had no symptoms which were referable to the colon. The recognition of diverticulosis of the colon in 7 per cent of 2,747 patients, who were examined roentgenologically, ordinarily would not be considered indicative of the true incidence of this condition among the general population, because this group includes largely those patients who had symptoms which were attributable to the colon. However, this rate of incidence coincides almost exactly with that observed by the pathologist. In 11 per cent of the diverticula of the colon there was inflammation and diverticulitis at the time of examination. In almost 13 per cent of the cases

of diverticulosis, there was a history that was suggestive of previous diverticulitis

TABLE I
Uncomplicated Diverticulosis
(72.60 per cent of total cases)

Situation	Number	Per cent
Sigmoid flexure	62	41.1
Sigmoid flexure and descending colon	26	17.2
Left half of colon	28	18.5
Entire colon	19	12.6
Ascending colon	3	2.0
Hepatic flexure	2	1.3
Ascending colon and sigmoid flexure	2	1.3
Cecum	2	1.3
Splenic flexure	2	1.3
Transverse colon	1	.7
Transverse colon and sigmoid flexure	1	.7
Left half of colon and cecum	1	.7
Right half of colon	1	.7
Right half of colon and sigmoid flexure	1	.7

Diverticulosis with history of diverticulitis
(12.98 per cent of total cases)

Sigmoid flexure	11	40.7
Sigmoid flexure and descending colon	10	37.0
Entire colon	4	14.8
Left half of colon	2	7.4

Total incidence of diverticulosis 85.58 per cent of total cases

Uncomplicated diverticulitis
(11.06 per cent of total cases)

Sigmoid flexure	19	82.6
Sigmoid flexure and descending colon	2	8.7
Descending colon	2	8.7

Diverticulitis with perforation
(2.40 per cent of total cases)

Sigmoid flexure	4	80.0
Sigmoid flexure and descending colon	1	20.0

Diverticulitis with obstruction
(0.96 per cent of total cases)

Sigmoid flexure	2	100.0
-----------------	---	-------

Total incidence of diverticulitis 14.42 per cent of total cases

Diverticula may be found in any portion of the gastrointestinal tract, and are not necessarily associated with similar abnormalities in any other portion. The preponderant occurrence of colonic diverticula in the sigmoid flexure is stressed by practically all writers on the subject. The relative frequency of involvement of various segments of the colon, as we found it, is given in table 1. The sigmoid flexure is most frequently involved in both diverticulosis and diverticulitis. Frequently, the involvement extends to the descending colon. The figures for diverticulosis roughly bear out the frequent statement that diverticula become more numerous toward the distal end of the colon.

The preponderant number of patients, who have diverticula of the sigmoid flexure, and who give histories that suggest diverticulitis, corresponds with the remarkably high incidence of active diverticulitis in the sigmoid flexure. When perforation or chronic obstruction occurred, it was invariably in the sigmoid flexure. One can only speculate as to the reasons for the high incidence of inflammatory changes in this situation. The theory of increased pressure in this region seems sound, but if one discards constipation and flatulence, as etiologic factors in the production of diverticula, it is difficult to explain why they should be effective in causing inflammatory changes.

INCIDENCE, SEX, AGE, AND BUILD OF INDIVIDUAL

The relative occurrence of diverticulosis and diverticulitis among the two sexes is of great interest. In the cases studied, diverticulosis was found as frequently among females as it was among males in the group of cases in which the condition was recognized clinically, although males predominated in the group of cases in which the existence of the lesions was first recognized by the pathologist. Males exceeded females in a ratio of 1.25 to 1 in the group of patients who gave a history of diverticulitis. Among the patients who had active diverticulitis at the time of examination, males outnumbered females 2.75 to 1. There were no females in the group with perforative or obstructive diverticulitis. All this would point to the fact that although uncomplicated diverticula of the colon affect women as frequently as they do men, the complications, and especially the serious complications, are more frequently observed among men. Alvarez's and Ascanio's study of 25,347 new patients, who registered at the clinic, indicated a ratio of males to females of 1.04 to 1. Our studies would seem to substantiate, therefore, the relative incidence by sex, which previously has been reported.

No instances of diverticulosis were found before the age of 30 years, among the cases studied. After the age of 30 years, the incidence of diverticulitis increased slowly in each half decade until that between the fifty-fifth and fifty-ninth years, which marked the peak of incidence for each sex. After this, the incidence decreased progressively. This is significant, inasmuch as Alvarez and Ascanio found that the curve, which represented the age of patients who registered at the clinic, reached its peak between the thirty-fifth and thirty-ninth years. There were only a few scattered cases of diverticulitis in which the patients were 50 years of age. After the age of 50 the distribution among men was practically equal in each half decade to the age of 70 years. There were only a few cases of diverticulitis among women, here the peak of incidence was in the seventh decade. The frequency of distribution of both conditions by decades for each sex is indicated in figures 1 and 2.

Reliable data in regard to height and weight of the patient were available in 51 cases of diverticulosis and in eight cases of diverticulitis. Comparison with a table of ideal weights revealed that there was practically an equal

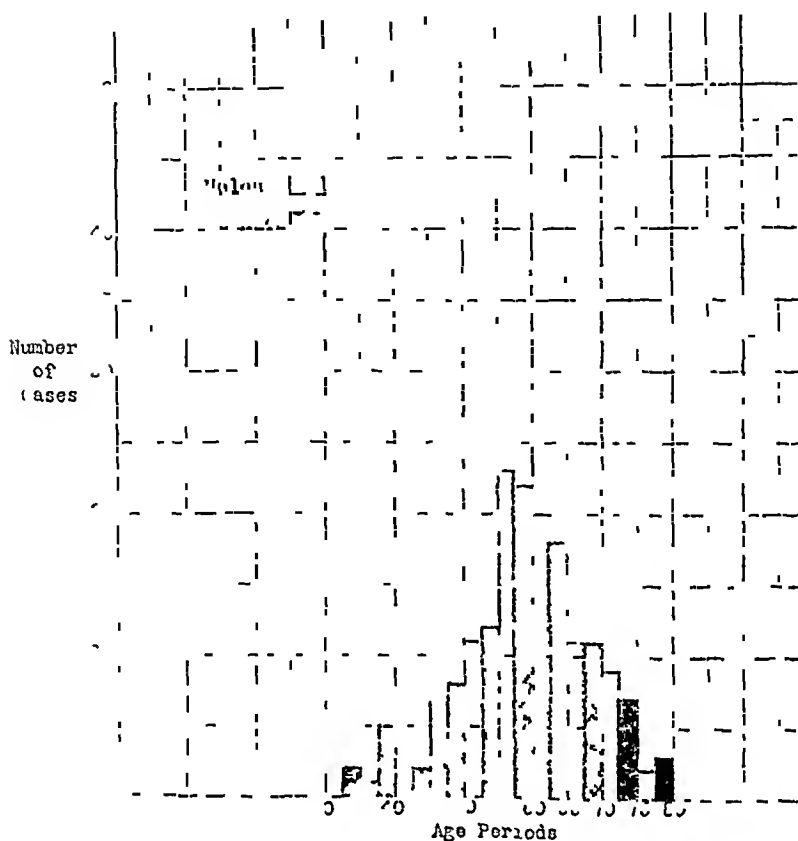


FIG 1 The incidence of diverticulosis by half decades

distribution of obesity and leanness Eighteen of the patients who had diverticulosis were of normal weight, nine were 10 pounds overweight, and seven were 10 pounds underweight Three of these patients were 20 pounds overweight and eight were a similar amount underweight, one was 30 pounds overweight and another was 40 pounds underweight Only one patient was 50 pounds overweight Among the patients who had diverticulitis, three were of normal weight, one was 10 pounds overweight and one was 10 pounds underweight Two were 20 pounds overweight and one was 20 pounds underweight

SYMPTOMS

The symptoms of diverticulosis in this series are enumerated in table 2 In the group of cases in which the sigmoid flexure was involved, constipation was present in 40 per cent while in 8 per cent there was diarrhea, which was present constantly in some, but only occasionally in other cases Flatulence was a symptom in 21 per cent of the cases and abdominal pain was noted in 18 per cent Pain was localized in the lower part of the abdomen, and varied in severity from a sense of fullness to cramping pains Six per cent of the patients had noticed a narrowing of the diameter of the stool,

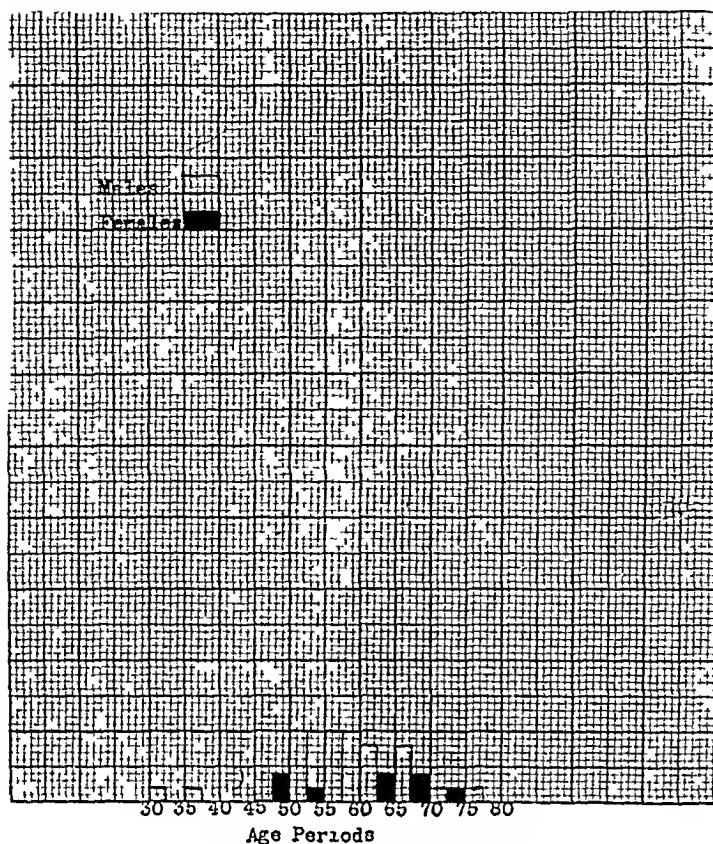


FIG 2 The incidence of diverticulitis by half decades

and an equal number had occasional rectal bleeding for which no cause was demonstrated. In 8 per cent of the cases, the clinical diagnosis was irritable intestine. This condition could account for the distress which was noted. Individuals who are severely constipated complain frequently of the smallness of their stools, and occasionally of slight bleeding. It can readily be seen that a majority of these cases of diverticulosis were devoid of symptoms which could be attributed to the diverticula.

Among the cases of diverticulosis which involved the sigmoid flexure and descending colon, 35 per cent of the patients complained of constipation of varying severity, and 31 per cent had mild diarrhea. Twenty-three per cent noted flatulence, and only 15 per cent had pain, which was a feeling of distress in the lower part of the abdomen and was relieved in half the cases by a bowel movement. Twelve per cent of the patients noted occasional rectal bleeding, which could not be accounted for by the presence of hemorrhoids.

In the cases of diverticulosis of the left half of the colon, constipation was noted in 29 per cent, diarrhea occurred in 14 per cent, and flatulence was present in 21 per cent. Abdominal distress, which was situated on the left side, was noted in two cases, or 7 per cent of the group. Constipation

TABLE II
Symptoms of Simple Diverticulosis

Situation	Total Cases	Constipation		Diarrhea		Abdominal Pain		Irritability		Flatulence		Blood	
		Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Sigmoid flexure	62	25	40	5	8	11	18	5	8	13	21	4	6
Sigmoid flexure and descending colon	26	9	35	8	31	4	15			6	23	3	12
Left half of colon	28	8	29	4	14	2	7			6	21		
Entire colon	19	8	42			1	5			1	5	1	5
Miscellaneous	16	9	56	1	6	2	12	2	12	2	12		

Symptoms of Diverticulosis with History of Diverticulitis

Situation	Total Cases	Constipation		Diarrhea		Abdominal Pain		Irritability		Flatulence		Blood	
		Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Sigmoid flexure	11	4	36	3	27	4	36			1	9		
Sigmoid flexure and descending colon	10	2	20	2	20	1	10			1	10		
Entire colon	4	2	50			1	25			1	25		
Left half of colon	2	1	50			1	50			2	100	1	50

was the principal symptom of the patients who had diverticulosis of the entire colon, it occurred in 42 per cent of the cases in this group. Only one patient (5 per cent of the group) complained of flatulence, and there was a similar incidence of lower abdominal pain and occasional rectal bleeding.

Of the remaining miscellaneous group, 16 in number, 56 per cent complained of constipation, which in one instance alternated with diarrhea. Only two complained of abdominal pain that could be attributed to the colon, and in each instance the patient was considered to have an irritable colon. Only two patients complained of meteorism.

In those cases of diverticulosis of the sigmoid flexure in which there was a history of diverticulitis, 63 per cent of the patients complained of irregularity of bowel movements, in 27 per cent of the cases there was some diarrhea, and in 36 per cent there was constipation. All of the patients, of course, gave a history of previous attacks of pain, but 36 per cent complained of abdominal pain at the time of examination, although there was then no evidence of diverticulitis. The pain was localized to the left lower quadrant of the abdomen, was dull in some cases, cramping in others, and was relieved to some extent by bowel movements. One patient, or 9 per cent, complained of flatulence. One patient had previously been operated on because of perforation and diverticulitis. Two patients, or 18 per cent, had no symptoms referable to the colon at the time of examination.

Among the patients who had diverticulosis of the sigmoid flexure and descending colon, and who presented a history of diverticulitis, 40 per cent complained of irregularity of bowel movements, there was an equal distribution of constipation and diarrhea. One patient, or 10 per cent, complained of gaseous distention, and in one case there was tenderness in the lower part of the abdomen. In two cases, or 20 per cent, colostomy had previously been performed for diverticulitis. Four patients, or 40 per cent of the total number, presented no gastrointestinal symptoms when examined.

Of the four patients who had diverticulosis of the entire colon and who gave a history of diverticulitis, two, or 50 per cent, presented no symptoms referable to the colon. Two, or 50 per cent, complained of constipation. One patient complained of gas, one had previously had diarrhea. Only one of these patients had pain at the time of examination. Of the two patients who had a demonstrated diverticulosis of the left half of the colon, and who gave a history of previous attacks of diverticulitis, one complained of tenderness in the left lower abdominal quadrant, which was relieved by a bowel movement or by the passage of gas, the other complained of constipation. Both patients had experienced discomfort from gas, and one had noted rectal bleeding.

The symptoms which were observed in the cases of diverticulitis are enumerated in table 3. The most common symptom among the patients, who had uncomplicated diverticulitis of the sigmoid flexure, was pain, which occurred in 17, or 89 per cent of the group. It was usually associated with irregularity of the bowels, either diarrhea or constipation, and a variable

degree of urgency of bowel movement. Frequently, the pain was relieved by bowel movement, and it occasionally was accompanied by rectal bleeding. Constipation occurred in 58 per cent of the entire group of cases, in one case there was an acute intestinal obstruction, diarrhea was noted in 26 per cent. The pain was localized to the left lower quadrant of the abdomen and was practically always intermittent and cramping in character. Occasionally, the pain extended to involve the entire abdomen. Three patients, or 16 per cent, complained of gaseous distention. In five, or 26 per cent of the cases, the patient complained of fever of variable degree, and in two cases there were chills as well. One patient had observed a lump in the left lower abdominal quadrant, there was a similar incidence of nausea and vomiting. Only three, or 16 per cent of the group, noted any urinary symptoms, in these cases there was a mild urgency of urination. Three patients had previously suffered attacks of diverticulitis.

In both cases of uncomplicated diverticulitis of the sigmoid flexure and descending colon, pain was noted in the left lower quadrant of the abdomen, both patients were constipated, and one had particularly observed a narrowing of the diameter of the stools, with a sense of obstruction and some gaseous distention. One had noticed some rectal bleeding. One had observed urinary frequency during the attacks. Both patients who had diverticulitis of the descending colon complained of pain in the left side of the lower part of the abdomen, and both were constipated. The patient who had diverticulitis of the rectosigmoid complained of pain in the lower part of the back, and was constipated.

All of the patients who had perforative diverticulitis of the sigmoid flexure of the colon complained of pain, which was localized in the left lower abdominal quadrant, cramping in character, accompanied by fever, and in half the cases, by chills. The cramps were often relieved by bowel movements, and sometimes by urination. Half of the patients complained of frequency and burning on urination. One patient was constipated and another had diarrhea. In one case there was a vesicosigmoid fistula. The one patient, who had perforating diverticulitis in the sigmoid flexure and descending colon, was constipated, and noted cramping pain and a tender mass in the left lower quadrant of the abdomen.

Both patients who had intestinal obstruction complicating sigmoid diverticulitis complained of pain in the lower part of the abdomen, which was cramping in character. This pain was accompanied in one case by diarrhea, in another case, by increasing constipation. One patient noted some rectal bleeding, the other had chills and fever.

EXAMINATION

Physical examination of the patients who had uncomplicated diverticulosis did not reveal any changes that could be attributed to the existence of this condition, the same was true of those who gave a history of previous diverticulitis. Among the 20 patients who had uncomplicated diverticulitis

of the sigmoid flexure, 10 had tenderness in the lower part of the abdomen, six had a mass in the lower quadrant of the abdomen or in the left side of the pelvis. Both patients who had uncomplicated diverticulitis of the sigmoid flexure and descending colon noted tenderness in the lower part of the abdomen, there was a palpable mass in one of these cases. Both patients who had diverticulitis of the descending colon and the single patient who had diverticulitis of the rectosigmoid disclosed tenderness in the left lower quadrant of the abdomen and a palpable mass. In all cases of perforative diverticulitis there was a tender mass in the left lower abdominal quadrant or in the pelvis, and the same was true of the patients who had chronic obstructive diverticulitis.

In the majority of writings on colonic diverticula, no mention is made of the value of proctoscopic examination in establishing the diagnosis. Only Fagge puts any faith in the method, he stated "more than a suspicion of diverticulitis may be established with the sigmoidoscope by the fixation and rigidity of the part of the pelvic colon affected." Proctoscopic examination was performed in 72 of the cases of diverticulosis, which we have studied. The occurrence of sacculation or fixation of the sigmoid flexure, or of demonstrable diverticula, confirmed the diagnosis in 15 cases, or 20 per cent of those examined. The observation of similar changes was made in 16 cases, or 64 per cent of the cases of diverticulitis. An interesting finding was the occurrence of polyps, three were situated in the rectum, six in the sigmoid flexure, and one in the rectosigmoid, making a total incidence of 14 per cent for the 72 patients who were examined by this method.

The most reliable method for demonstration of colonic diverticula is the roentgenologic examination. By the combined use of roentgenologic and proctoscopic examinations, practically all cases of diverticulosis can be detected, and most of these cases are impossible of clinical diagnosis. Certainly, although a clinical diagnosis of diverticulitis can usually be made with a fair degree of certainty, examination by a competent radiologist is the most accurate method of differential diagnosis in difficult cases. The opinion of the radiologist may be taken as of greater value than that of the clinician, or even that of the surgeon, who may actually have examined the lesion. There is some difference of opinion in regard to the relative value of the barium meal and the barium enema in roentgenologic examination, we prefer the latter.

RELATION OF DIVERTICULOSIS, DIVERTICULITIS AND CARCINOMA

The relationship of diverticulitis to carcinoma of the colon has long been a matter of dispute. Early observers felt that diverticulitis was definitely an etiologic factor, but more recent writers seem to hold a view similar to that which was expressed by Rankin and Brown who found carcinoma in only four of 227 cases of diverticulitis which they studied. They expressed the opinion that the relationship of diverticulitis to carcinoma is probably

incidental rather than actual. We found malignancy of the colon in 6 per cent of the cases in which diverticula of the colon were discovered by clinical examination, the association was noted only among the patients who had diverticulosis, and who did not give a history suggestive of diverticulitis. In only seven of the 13 cases in which it was noted, was the malignancy in that portion of the colon in which the diverticula were found.

TREATMENT AND PROGNOSIS

The best treatment for diverticulosis consists of the avoidance of constipation and irritation, this is best accomplished by the use of a diet, which is bland and non-constipating, and which is free from residue. Mineral oil should be administered orally as a lubricant.

It is our practice to administer atropine in the form of tincture of belladonna to help relieve and avoid spasm. All cases of diverticulitis are associated with some peridiverticulitis, and the milder degrees of this change do not materially alter the outlook for the patient. The occurrence of the more serious complications, such as the formation of abscesses, with or without perforation, the formation of fistulas, peritonitis, and the occurrence of obstruction, which cannot be relieved by medical measures, constitute a clear indication for conservative surgery. Once such complications occur, the future is fraught with danger unless the intestine can be resected. However, some patients who had suffered complications, which have demanded colostomy, have recovered, the colostomy has been taken down, and no further trouble has been experienced.

The prognosis of simple diverticulosis is good, although some likelihood of inflammation exists. The prognosis of uncomplicated diverticulitis is rather good, most patients can be relieved by the medical measures which have been described previously.

COMMENT

It is difficult to determine the incidence of diverticula of the colon among the general population, there is a wide variation in the reports of necropsy. Although in the year 1933 the condition was recognized among only 0.4 per cent of the registrants at the clinic, it was found in almost 7 per cent of the necropsy reports for the same period. The diagnosis of diverticulosis depends on the roentgenologic examination. During the year which is covered by this investigation, 7 per cent of 2,984 patients, who were examined roentgenologically after they had received a barium enema, were discovered to have diverticulosis. This would suggest that these figures indicate the approximate incidence of diverticulosis. Diverticula are generally thought to affect males more often than they do females. In this group it was found that diverticulosis was evenly distributed among the two sexes, although diverticulitis, and particularly the complications of diverticulitis, occurred most frequently among males. It would seem, therefore, that colonic di-

verticula, like hypertension and many other conditions, are to be viewed with greater concern when they affect men than when they affect women. Although the occurrence of diverticula among children has been described, it is uncommon before the age of 40 years, and most common in the latter half of the sixth decade and first half of the seventh decade.

The etiology of colonic diverticula is still a matter of speculation. Among the etiologic factors, constipation and flatulence have been named, but the incidence of these symptoms has not been greater in the cases which we have studied than it would be among the general population. It is probable that obesity does not act as an etiologic factor, the majority of our patients were of normal weight.

It is probable that there is an inherent weakness of the muscular layer of the intestinal wall, whether this is inherited or acquired has not been determined. It is generally admitted that diverticula occur largely during the years of degenerative changes in the body. As previously stated, diverticulitis, or even diverticulosis, is exceedingly rare before the patient is 40 years of age. The possibility of the formation of diverticula as a senile change in an inherently weak muscular wall of the colon then suggests itself. The muscular weakness occurs in disseminated places, and affects patients who have been subjected to colonic strain and stress.

Diverticula are found with increasing frequency in the lower part of the intestinal tract. Diverticula are comparatively rare in the right half of the colon, and most common in the sigmoid flexure.

We have attempted in table 4 to classify the varieties and complications of diverticula of the colon as found in this series as well as in the literature. As can be seen, we consider that the so-called pre-diverticular stage is really a stage of diverticulosis, and we have found that a number of patients who had diverticulosis gave a history of previous diverticulitis. Diverticulitis, of course, may be acute, recurrent, or chronic. Peridiverticulitis, which frequently occurs in diverticulitis, may be simple or it may be associated with a variable degree of enterospasm. It is probable that peritonitis frequently occurs with diverticulitis but is usually not manifest, diverticulitis may be associated with abscess, or with perforation. Entero-visceral or entero-cutaneous fistulas may follow perforation. Rarely, metastatic suppuration occurs. With the healing of diverticulitis, adhesions may occur but they rarely produce obstruction. Although carcinoma of the colon may affect patients who have colonic diverticula, the association is probably accidental.

There are not any symptoms which are characteristic of diverticula, and recognition is dependent upon roentgenologic or proctoscopic examination. In a certain number of cases of diverticulosis, a history of previous attacks of diverticulitis can be elicited. The cardinal symptom of diverticulitis is pain, which usually is associated with irregularity of bowel movements, and which often is relieved by bowel movements. Pain is usually localized in the left lower quadrant of the abdomen, is of variable severity, and usually is intermittent and cramping. It may be accompanied by distention, chills

TABLE IV

Varieties and Complications of Diverticula of the Colon

- I Diverticulosis
 - A Pre-diverticular stage of Spriggs and Marker
 - B Stage of formed diverticula
 - 1 Asymptomatic
 - 2 Symptomatic
 - a History of previous attacks of diverticulitis
- II Diverticulitis
 - A Acute
 - 1 Simple
 - 2 Complicated
 - a Peridiverticulitis
 - aa Simple
 - bb Enterospasm
 - 1 Without obstruction
 - 2 With acute obstruction
 - a Partial
 - b Total
 - 3 With chronic obstruction
 - b Peritonitis
 - aa Local
 - 1 Non-suppurative
 - 2 With abscess
 - a Perforation
 - aa General peritonitis
 - bb Fistulae single or multiple
 - 1 Entero-intestinal
 - 2 Entero-vesical
 - 3 Entero-cutaneous
 - bb General
 - c Resulting from lodgment of foreign body
 - d Metastatic suppuration
 - aa Septicemia
 - bb Suppurative pylephlebitis or portal pyemia
 - cc As a focus of infection
 - B Recurrent
 - C Chronic
 - 1 Simple
 - 2 Complicated
 - a Peridiverticulitis
 - aa Enterospasm
 - bb Hyperplasia with obstruction
 - b Mesenteritis
 - c Peritonitis
 - aa Acute
 - bb Recurrent
 - cc Chronic
 - 1 Adhesions
 - a With or without angulation and obstruction

and fever, dysuria, and urinary frequency. When perforation occurs pain is more severe, often excruciating, and there are fever and chills. Urinary symptoms are frequent in the group with perforation, particularly if the perforation occurs anteriorly. When obstructive tumefaction occurs, there may be either constipation or diarrhea.

Physical examination of patients, who have diverticulosis, does not reveal any significant signs that can be referred to the colon. Patients who have diverticulitis usually have tenderness in the left lower quadrant of the abdomen, and often present a palpable mass. When perforation or obstruction occurs in diverticulitis, there is always a palpable mass, in the acute

phase, the tenderness may be so marked as to prevent adequate examination. Proctoscopic examination is of definite value, especially in cases of diverticulitis, in the acute phase of which one might fear to give a barium enema. Experienced observers can make a positive diagnosis by this method in 64 per cent of the cases. Roentgenologic examination is, of course, the most accurate means at our disposal for the detection of these lesions.

BIBLIOGRAPHY

- 1 ABBE, R. A case of sigmoid diverticulitis simulating malignancy demonstrated by radiograph operation and specimen. *Med Rec*, 1914 lxxvi, 190-191.
- 2 ALVAREZ, W. C., and ASCANIO, H. Age and sex distribution of patients at The Mayo Clinic. *Human Biology*, 1930, ii, 185-198.
- 3 BEER, E. Some pathological and clinical aspects of acquired (false) diverticula of the intestine. *Am Jr Med Sci*, 1904, cxviii, 135-145.
- 4 BELL, F. G. Diverticulitis. *Jr Col Surg Austral*, 1929, ii, 226-232.
- 5 BELL, E. T. A textbook of pathology. 1930. Lea and Febiger, Philadelphia, pp 477-478.
- 6 CASE, J. T. Roentgen study of multiple diverticula. *Am Jr Roentgenol and Radium Therap*, 1929, xxi, 207-220.
- 7 CRUVEILHIER, J. Quoted by Case.⁶
- 8 ERDMANN, J. F. Diverticulitis and diverticulosis. *Jr Am Med Assoc*, 1932, xcix, 1125-1128.
- 9 FAGGE, C. H. Diverticulitis. *New Zealand Med Jr*, 1932, xxi, 65-75.
- 10 FISCHER, M. H. False diverticula of the intestine. *Jr Exper Med*, 1900, v, 333-352.
- 11 GIFFIN, H. Z. The diagnosis of diverticulitis of the large bowel: a clinical review of twenty-seven cases. *Jr Am Med Assoc*, 1912 lxx, 864-866.
- 12 GIFFIN, H. Z., and WILSON, L. P. A case of carcinoma on diverticulitis of the sigmoid. *Am Jr Med Sci*, 1909, cxixiii, 661-666.
- 13 GRASER, E. Über falsche Darmdivertikel. *Verhandl d Gesellsch deutsch Naturf u Aerzte*, 1899-1900, lxxi, 14-15.
- 14 LITRE. Quoted by FINNEY, J. M. T. Diverticulitis and its surgical treatment. *Proc Interstate Post-Graduate Med Assembly of N Am*, 57-65, 1928.
- 15 LOCKHART-MUMMERY, J. P., and HODGSON, H. G. Observations on diverticula of the colon and their sequelae. *Brit Med Jr*, 1931, i, 525-527.
- 16 MAYO, W. J. Diverticula of the sigmoid. *Trans Am Surg Assoc*, 1930 xlviii, 301-305.
- 17 MAYO, W. J., WILSON, L. B., and GIFFIN, H. Z. Acquired diverticulitis of the large intestine. *Surg Gynec and Obst*, 1907, v, 8-15.
- 18 MOYNIHAN, B. G. A. Mimicry of malignant disease in the large intestine. *Edinburgh Med Jr*, 1907, xxi, 228-236.
- 19 RANKIN, F. W., and BROWN, P. W. Diverticulitis of the colon. *Surg, Gynec and Obst*, 1930, l, 836-847.
- 20 TELLING, W. H. M. Acquired diverticula of the sigmoid flexure, considered especially in relation to secondary pathological processes. *Lancet*, 1908, i, 843-850.
- 21 WILSON, L. B. Diverticula of the lower bowel, their development and relationship to carcinoma. *Ann Surg*, 1911, liii, 223-231.

INTERNAL MYXEDEMA; REPORT OF A CASE SHOWING ASCITES, CARDIAC, INTESTINAL AND BLADDER ATONY, MENORRHAGIA, SECONDARY ANEMIA AND ASSOCIATED CAROTINEMIA

By ROBERTO F ESCAMILLA, M D , H LISSER, M D , F A C P , and
H CLARE SHEPARDSON, M D , F A C P , *San Francisco, California*

THE classical picture resulting from diminished thyroid activity has long been recognized. But the fact that this endocrinopathy is generalized, involving the internal organs as well as the external covering and configuration of the body, is not so widely appreciated. Thus, alterations in the skin and hair, together with mental sluggishness, are relatively common findings. Occasionally cardiopathies occur for which no morbid factor other than an insufficient thyroid function can be found. More rarely abdominal ascites occurs as part of the syndrome of myxedema. Yet the literature contains a few reports of this finding for which no other etiology was demonstrated, and which disappeared under administration of thyroid substance.

In one such case, recently cited by Evans,¹ various chemical studies were made of the abdominal fluid. In addition, atony of the bladder (discovered accidentally when an attempted abdominal paracentesis yielded urine from a distended atonic bladder) was noted for the first time.

Our patient is considered of sufficient interest to report because she presented so many of the internal manifestations of myxedema with a paucity of the external signs. Both abdominal ascites and atony of the bladder were present. Chemical studies were made of the abdominal fluid in order that the figures obtained could be compared with those resulting from similar studies by Evans.

No other cause for any of the findings could be discovered, and the low basal metabolic rate, together with the marked improvement that resulted from the administration of thyroid substance apparently makes the diagnosis of hypothyroidism indubitable.

CASE REPORT

O J, a 45 year-old, white, American farmer's wife was first admitted to the University of California Hospital on August 25, 1933.

Chief complaint—bloating and gas

Family history—one sister had a carcinoma of the stomach

Marital history—revealed that she had had four children. Two of these died in infancy and two were living and well. In addition there had been four miscarriages and the most recent pregnancy, two years before, had terminated in a still-birth.

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

From the Department of Medicine of the University of California Medical School, San Francisco, Calif

Past history showed pneumonia and smallpox in childhood, the usual childhood diseases, frequent sore throats prior to a tonsillectomy 19 years before, and a dry pleurisy six years before. She had been subject to attacks of migraine until 12 years before, and had always had very profuse menstrual periods lasting seven to eight days.

Present illness began 10 years prior to entry with the gradual development of pallor, weakness, sore and stiff joints, and finally ascites and edema of the ankles and face. Eight years before, she had entered a hospital for treatment. While there her abdomen was tapped, yielding a large amount of straw-colored fluid. She was told that her blood tested "60" and was discharged after five weeks with instructions to take a low protein diet. Since that time she had noted gradually progressive slowing of mental and physical activity. Her memory became poor and her speech slow. She also noted dry skin, lack of perspiration, intolerance to cold, and some loss of eyebrows and hair. For four or five years there had been increasing constipation, and she began to be troubled by bloating and gas. For two years she had had dull upper abdominal pain which affected her appetite, during this time she had lost 13 pounds. Her diet contained large quantities of vegetables, frequently carrots. The joint-pains persisted, her menstrual periods continued to be profuse (lasting eight to ten days) although somewhat irregular during the preceding year.

She finally visited the University of California Out-Patient Department where her basal metabolic rate was found to be minus 37 per cent and the blood hemoglobin (Sahli) 55 per cent (100 per cent equals 14.0 grams per 100 c.c.), with a red cell count of 2,700,000 per cu. mm. Gastric analysis after an alcohol meal showed free acid to 47 units and total acid to 57 units. She was then sent into the hospital.

Physical examination disclosed a patient who moved slowly and whose speech was slow and deliberate. The skin had a pale, slightly icteric tint, and was dry, cold, and somewhat rough. The hair was thin, dry, and scanty in the axillae. The eyebrows were sparse, especially the outer halves. The thorax was poorly clothed and the breasts atrophic. The heart showed enlargement both to the left and the right, the sounds were slow and of poor quality. There was a faint systolic murmur at the apex. Blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. The abdomen was distended both by gas and fluid, and there was marked diastasis recti with an umbilical hernia. No viscera or masses were palpable. Pelvic examination revealed no abnormality except a lacerated cervix and rectal examination showed internal hemorrhoids. There was slight pitting edema over the anterior tibial surfaces of the legs. There was no thickening of the subcutaneous tissues nor were there any of the fat pads commonly noted in hypothyroidism.

LABORATORY DATA

Basal Metabolic Rate Minus 37 per cent and minus 41 per cent

Blood Hemoglobin (Sahli) 50 per cent, red blood cells 3,160,000 per cu. mm., white blood cells 4,400 per cu. mm., with a normal differential count

Urine Specific gravity 1.010, albumin, very slight trace, sugar, 0, sediment, showed an occasional pus cell

Stool Negative for ova, parasites and occult blood

Phenolsulphonephthalein Kidney Function Test 50 per cent excretion in 380 c.c. of urine 2 hours and 10 minutes after intramuscular injection

Blood Kahn Negative

Plasma cholesterol—238 mg. per cent

Serum proteins—Total 6.46 gm. per cent, albumin, 3.90 gm. per cent, globulin, 2.56 gm. per cent, ratio, 1.52

Sugar (fasting) 70 mg. per cent

Non-protein nitrogen 29.8 mg. per cent

Chlorides (as NaCl in plasma) 523 mg. per cent

medication was started, had dropped to 57 kilograms (125.4 pounds) on discharge 20 days later

At this time there was very little symptomatic improvement and the patient was instructed to increase her thyroid dosage to 0.065 gm four times daily. She was discharged from the hospital on September 13, 1933.

Interval History The patient returned to the clinic one month after leaving the hospital stating that there had been marked improvement in general well-being. Her skin was smoother and she perspired occasionally. She had had one menstrual period which had lasted only three or four days and had been relatively scanty in contrast to her former menorrhagia. Her appetite had improved and she had ceased losing weight.

She now appeared more alert, though still pale. There was no icterus. The heart had diminished to normal size, the rate was 84, and the sounds were forceful in character. No ascites or abdominal distention could be found. There still remained slight edema of the ankles.

LABORATORY DATA

Basal Metabolic Rate Plus 7 per cent (minus 41 per cent before treatment)

Plasma Cholesterol 144 mg per cent (238 mg per cent before treatment)

Blood Hemoglobin (Sahli) 55 per cent, red blood cells 2,810,000 per cu mm, white blood cells 6,100 per cu mm

Urine Negative, specific gravity 1.006. Sediment showed a rare white blood cell.

Roentgenogram of the chest revealed a marked diminution in heart size (4.9 cm less in the transverse diameter) with pulsations of good tone.

Electrocardiogram Rate 80, P-R interval 0.16 second, QRS complexes were of greater amplitude and there was marked improvement in the T-waves.

Second Hospital Admission The patient was readmitted to the hospital for further study on November 20, 1933, one month after her last visit to the clinic and two months after her first discharge from the hospital.

She stated that the improvement had been maintained, although her constipation was unchanged. She still noted palpitation occasionally on exertion and ankle edema late in the day.

Physical examination was essentially as before. The skin had a more yellow tint. The heart was normal in size to percussion and the sounds were of good quality, rate 72. The abdomen showed moderate distention. There was no ascites and no edema of the extremities.

LABORATORY DATA

Basal Metabolic Rate Plus 3 per cent

Blood Hemoglobin (Sahli) 45 per cent, red blood cells 2,800,000 per cu mm, white blood cells 6,950 per cu mm

Urine Specific gravity 1.010, albumin 0, sugar 0, sediment showed an occasional white blood cell.

Blood Plasma cholesterol 151 mg per cent

Serum proteins Total, 6.12 gm per cent

Albumin, 4.18 gm per cent

Globulin, 1.94 gm per cent

Ratio 2:15

Third Admission to Hospital—August 30, 1934 Six and one-half months after her last visit, the patient was readmitted to the hospital as an emergency

She had been feeling quite well and doing all of her housework until two months before. At that time she undertook some part-time work in a cannery near her farm, which after a short while was increased to full-time. This work in addition to her household duties made a daily schedule of 16 to 17 hours labor. Five weeks before entry, after two weeks of this exhausting regime, she was awakened one night by a feeling of nausea and a dull generalized abdominal ache. She developed some weakness and anorexia and noted mucus in her stools. Then she felt better for two or three days, but on trying to return to work, developed severe epigastric and right lower abdominal pain accompanied by nausea and protracted vomiting. She was

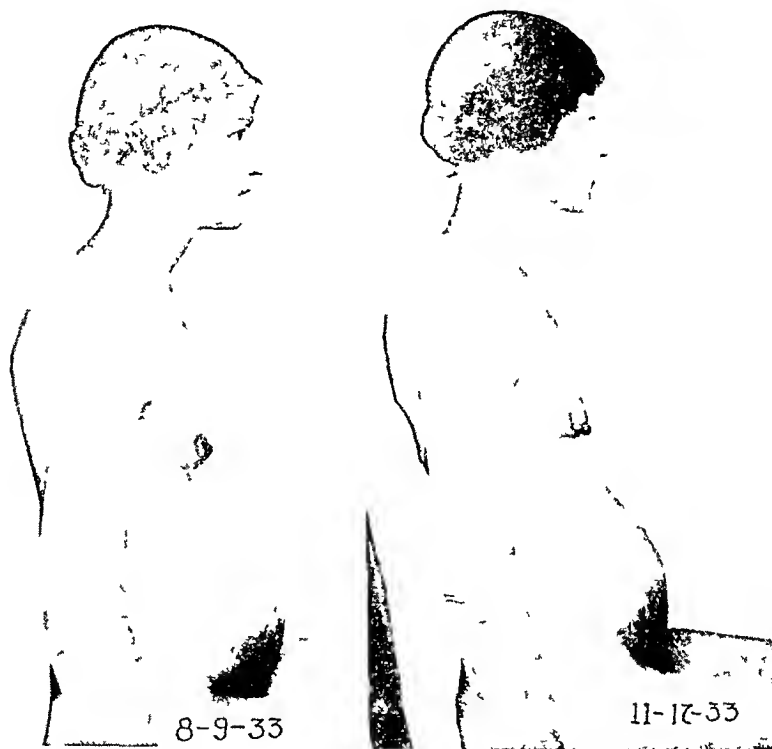


FIG 1 Comparative views of the patient showing her general appearance and the diminution in abdominal distention after treatment was instituted

said to have regurgitated food eaten 36 hours previous. She was hospitalized for eight days, obtaining gradual relief from enemata and cathartics. Once again she returned to work. However, all the severe symptoms recurred and, after two weeks of nausea and frequent vomiting, she was again brought to San Francisco and admitted to the University of California Hospital. After the onset of these acute symptoms five weeks before she had taken thyroid only irregularly, and at the time of entry she had had none for four weeks.

On examination she was still nauseated, vomiting frequently, and obviously dehydrated. The abdomen showed visible peristalsis and tenderness in the right upper quadrant.

Some improvement resulted from the administration of fluid parenterally and glucose intravenously so that four days later a barium enema was given, followed by barium orally. Under the roentgen screen there was evidence of partial obstruction of the jejunum.

A subcutaneous injection of Pitressin caused a marked increase in visible peristalsis followed by a reproduction of the nausea and abdominal pain. It was then decided to perform an exploratory laparotomy which was done on September 7, 1934, by Dr. Leon Goldman.

On opening the abdomen a small amount of colorless free fluid escaped. The small and large intestines appeared normal throughout. The appendix, liver, kidneys, and pancreas were apparently normal. The gall-bladder was slightly thickened, there were a few periduodenal adhesions. The uterus was somewhat enlarged and soft. The appendix was removed.

The postoperative course was uneventful. A menstrual period started two days later at the regular interval. Pelvic examination immediately afterward was normal and a Friedman test for pregnancy was negative. The conclusion was reached that the enlarged and soft uterus noted at operation was due to pre-menstrual congestion.

Since the patient had not had any thyroid substance for over five weeks, it was planned to utilize this opportunity as a control period and as soon as her condition warranted, to repeat most of the laboratory studies. Unfortunately she was not directly under the authors' care, thyroid was prescribed and she received 0.065 gm eight times in three days before it was discontinued. Basal rate taken then was 9.3 per cent minus. After another week without thyroid the following laboratory work was done:

Basal Metabolic Rate Minus 22 per cent

Blood hemoglobin (Sahli) 85 per cent, red blood cells 4,700,000 per cu mm,
white blood cells 10,700 per cu mm

Plasma cholesterol 200 mg per cent

Serum proteins Total, 4.8 gm per cent

albumin, 3.22 gm per cent

globulin, 1.57 gm per cent

Ratio 2.05

Icterus index 11

Carotin Negative

Glucose Tolerance Test Blood sugar, fasting, 82 mg per cent

30 minutes, specimen lost

60 minutes, 137 mg per cent

120 minutes, 84 mg per cent

Rose Bengal Liver Function Test

Specimen I (8 minutes), 78 per cent retention

Specimen II (16 minutes), 60 per cent retention

Residual Urine—500 cc

Roentgen films and fluoroscopy of the chest showed the heart to be normal in size and the beats of good tone.

Electrocardiogram showed a rate of 60 per minute. The P-R interval was 0.18 second. The QRS complexes and T-waves were of small amplitude.

The body temperature tended to be low as did the rate of the pulse and respiration.

The patient was discharged on September 20, 1934, with instructions regarding limited activity and the resumption of thyroid substance, 0.065 gm twice daily. This dose, however, was to be increased gradually as indicated.

DISCUSSION

Ascites The rarity of ascites as a manifestation of myxedema has already been noted. However, several reports can be found in the literature. Mussio-Fournier³ reported five cases, two of which had associated hydrothorax. He quotes Nothnagel as publishing a similar case. Marsh⁴

O J Outline of Laboratory Work

B M R	8/25/33	9/25/33	10/23/33	11/20/33	1/16/34	2/16/34	9/19/34
Plasma Cholesterol	40% minus	26% minus	7% plus	3% plus	—	1% minus	22% minus
Icteric Index	238 mg %	134 mg %	144 mg %	151 mg %	—	—	200 mg %
Blood Carotin	15	8	—	11	—	—	11
Blood—Hgb	2 plus	Neg	—	Neg	1 plus	—	Neg
RBC	50%	47%	55%	45%	76%	80%	85%
WBC	3,160,000	3,240,000	2,810,000	2,800,000	4,660,000	4,450,000	4,280,000
Urine—Albumin	4,400	—	6,160	6,950	6,800	—	7,120
Residual Urine	2 plus	Neg	Neg	Neg	—	—	Neg
Rose Bengal Test—Retention—	100 c c	—	—	45 c c	—	—	500 c c
I	62%	—	—	53%	—	—	78%
II	44%	—	—	32%	—	—	60%
EKG—Rate	51	60	80	60	—	—	60
P-R Interval	0 22 sec	0 22 sec	0 16 sec	0 19 sec	—	—	0 18 sec
Glucose Tolerance Test—	77 mg %	—	—	108 mg %	—	—	82 mg %
I	137	—	—	186	—	—	—
II	156	—	—	218	—	—	137
III	148	—	—	141	—	—	84
IV	90/50	90/48	—	114/56	120/74	110/60	120/70
Blood Pressure	63 2 Kg	57 0 Kg	57 5 Kg	60 1 Kg	64 3 Kg	64 4 Kg	52 1 Kg
Weight	36°C	36 5°C	—	37°C	—	—	36°-37°C
Temperature	50-60	70	84	80	84	72	50-60
Pulse	18	20	—	20	—	—	11-17
Respirations	—	—	—	—	—	—	—

CHART 1 Outline of the laboratory findings during the thirteen-month period of observation

reported another case. Six questionable instances were presented by Davidson⁵ who labeled them "thyroid nephrosis." Beretervide and Herrera⁶ report a case which seems typical clinically but whose basal metabolic rate was only minus 15 per cent. The recent report of Evans¹ has already been referred to.

The finding of ascites is especially interesting in this patient because of its reported presence eight years before. Although the second abdominal paracentesis was unsatisfactory and yielded only 150 c c of fluid, physical signs indicated the presence of a much larger amount. These signs completely disappeared after seven weeks of thyroid-therapy and there was no further evidence of fluid until the exploratory laparotomy revealed a small amount after four weeks without thyroid.

Other causes for the ascites could be excluded. The duration of eight years made it improbable that either carcinoma, cirrhosis or tuberculosis was responsible. This was borne out by the negative findings at exploration. No evidence of nephritis was found—the only urinary abnormality being an albuminuria which disappeared under thyroid-therapy. The proteins of the blood serum were found to be normal both before and after the beginning of treatment, so osmosis was probably not a factor. The possibility of cardiac decompensation with venous congestion was an important one, especially in view of the enlarged heart found on admission. However, the venous pressure was normal in four determinations and no other evidences of congestive failure were found. The above findings, combined with the facts that the ascites vanished on thyroid-therapy, and reappeared after thyroid was omitted, make it reasonable to assume that hypothyroidism was the etiologic factor.

Evans¹ after using approximately similar precautions likewise reached the conclusion that the ascites in his patient was of myxedematous origin. It is interesting, therefore, to compare the properties and chemical content of the fluids obtained by him and us. The following table also includes the recorded findings on the fluids from the patients reported by Beretervide and Herrera⁶ and by Mussio Fournier³.

The specific gravity was high in Evans' case. In the case of Beretervide and Herrera the strongly positive Rivalta also classes the ascitic fluid obtained by them as an exudate. However, in our patient the fluid had a relatively low specific gravity. Mussio Fournier reports a negative Rivalta in one case and definitely calls the fluids from three of his other cases transudates. Evans found a relatively high total protein and Beretervide and Herrera obtained a high figure for albumin content. In the case here reported the proteins were lower.

Epstein⁷ found the average protein content in nine ascitic fluids due to cardiac decompensation to be 3.3 gm per cent. Salvesen and Linder⁸ reported values of 2.6 and 2.2 gm per cent in two cases of cardiac ascites. Fooid, Youngberg and Wetmore,⁹ after examining the ascitic fluid from 10 cases of cirrhosis and eight of cardiac decompensation obtained an

	O J (1933)	Evans (1932)	Beretervide and Herrera (1932)	Mussio Fournier (1925)
Specific Gravity	1 012	1 020	Strongly positive Rivalta	1 negative Rivalta
Cells	75 mononuclear leukocytes 25 polynuclear leukocytes 4,400 red blood cells	77 mononuclear leukocytes 335 red blood cells	85 per cent lymphocytes	3 "transudates" Endothelial cells
Total Protein	3 88 gm %	5 1 gm %	7 6 gm % (by refractometer method)	
Albumin	2 31 gm %	2 9 gm %		
Globulin	1 57 gm %	2 2 gm %		
Non Protein Nitrogen	23 mg %	23 mg %		
Chlorides (as NaCl)	648 mg %			
Cholesterol	96 mg %			
Sugar	112 mg %			

average specific gravity of 1 012 and an average protein content of 1 32 gm per cent and 1 69 gm per cent respectively in the two groups Macheboeuf and Fethke¹⁰ report protein values averaging 4 22 gm per cent in the ascitic fluid of two patients with cardiac disease and 1 65 gm per cent in two patients with alcoholic cirrhosis The value of 3 88 gm per cent reported in this case is therefore higher than the average findings in transudates, but not as high as that reported by Evans¹

The values for non-protein nitrogen, chlorides, cholesterol, and sugar fall within the average range found in ascites due to cirrhosis and cardiac decompensation (Foord et al⁹ and Macheboeuf and Fethke¹⁰)

Foord and associates⁹ have noted that in fluids with high specific gravity there is a proportional increase in the protein, and the Rivalta test becomes increasingly positive When this fact is applied to the findings in the table above, it is apparent that there is considerable variation in the composition of ascitic fluid recovered from patients with myxedema Whether or not this fluid is true "myxedematous fluid" is a speculative question, but if so, then one of the characteristics of such fluid is a varying composition

Atony of the Bladder The association of urologic symptoms with myxedema was commented on long ago However, Beck,¹¹ in 1927, studied 100 cases particularly from this standpoint He noted the frequency of nocturia, pollakiuria, dysuria oliguria and incontinence, and stated that the urinary sediment usually showed large numbers of epithelial cells from the bladder and frequently pus The accidental discovery by Evans,¹ of atony of the bladder with residual urine, gives an obvious explanation for all these symptoms and signs The atony in his patient was so marked that the bladder had not been able to empty itself even after preliminary catheterization with a short catheter

Although the atony in our case was not marked, only 100 c c of residual urine being obtained at first, there was definite improvement on thyroid-therapy. Three months after thyroid was started the residual had decreased to 45 c c. The postoperative residual of 500 c c was considered as resulting largely from the surgical procedure.

It seems probable that more frequent observations will reveal this to be a common finding in hypothyroidism. In view of the frequent and characteristic cardiac and intestinal atony, it is not so much surprising that bladder atony also occurs, but that this phenomenon was not noted many years ago.

Cardiac Atony. There have been numerous case reports and discussions in the literature since Zondek¹² first described "Das Myxodemherz" in 1918. Recent excellent reviews of this subject can be found in papers by Lissner and Anderson,¹³ Ayman, Rosenblum and Falcon-Lesses,¹⁴ Gallagher,¹⁵ and Lerman, Clark and Means.¹⁶ The original description by Zondek is of a symmetrically enlarged flabby heart with slow feeble action under the fluoroscope, but without evidences of decompensation. Many of the reported cases are of this type. Under thyroid-therapy these hearts shrink to normal.

In 1925 Fahr¹⁷ reported a patient in whom congestive failure was a marked feature and another group of reported cases belongs to this class. Thyroid in such cases results in great improvement.

A third group, however, shows an accompanying advanced arteriosclerosis. Attempts at thyroid-therapy, by raising the metabolism and cardiac rate, place an increased strain on the myocardium which may result in marked cardiac embarrassment and even coronary thrombosis. Christian,¹⁸ and Sturgis and Whiting¹⁹ called attention to this possibility.

Fishberg,²⁰ Christian,¹⁸ and Duden²¹ have called attention to the high incidence of early arteriosclerosis in myxedema, while Thompson, Dickie, Morris and Hilkevitch²² have noted the high incidence of hypertension. It is, therefore, possible that the three groups of cardiac complications outlined above (i.e., (1) atony without decompensation, (2) atony with decompensation and (3) atony with decompensation and advanced arteriosclerosis) are progressive stages of the same process. Apparently the important etiological factor in the first group is hypothyroidism, but as the cardiac picture progresses, arteriosclerosis plays a gradually increasing rôle.

The heart findings in the case here reported place it in the first group of atony without decompensation. Roentgen-ray examination showed the heart to be enlarged in all chambers. The rate was slow and by fluoroscopy the myocardium appeared flabby, the beats feeble and of poor tone. Auscultation disclosed the heart sounds to be of poor quality. After six weeks of thyroid-therapy the heart had diminished in size in all diameters, and the transverse diameter was decreased by 4.9 cm (figure 2). The rate had increased and the beats were seen to be of good tone. There was

a coincidental improvement in the quality of the heart sounds. No loss in tone could be detected after thyroid had been discontinued for five weeks, although the rate was slower.

The electrocardiographic changes were fairly pronounced, although not as marked as many of those which appear in the literature. The changes most frequently noted are low, diphasic, or inverted T-waves in one or more leads. According to Thatcher and White²³ and Lissner²⁴ this occurs most frequently in Lead II, but Fahr²⁵ states that it is more common in Lead I. Low electromotive force resulting in decreased amplitude of the QRS complexes has been stressed by many writers, and Fahr²⁵ has frequently noted

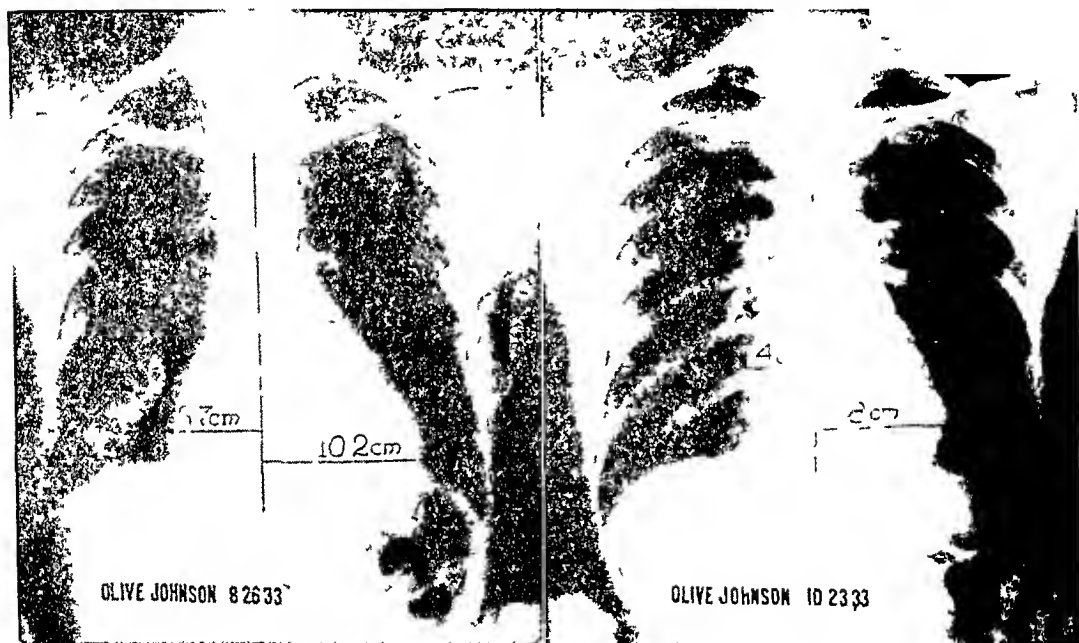


FIG 2 Typical myxedema heart with enlargement of all chambers. The shrinkage in heart size under therapy is quite apparent, with a difference of 4.9 cm in transverse diameter after two months of treatment. Under the fluoroscope the beats were of markedly improved tone at the second examination.

a negative QRS complex in Lead III. Absent or diminished P-waves were first noted by Zondek¹² in his original paper and have been reported frequently since. Slurring of the QRS complexes and prolongation of the P-R interval are other changes that have been occasionally noted. The changes, however, have been variable in the reported cases.

The effect of the increased resistance of the skin in myxedema has been a source of conflicting reports. Nobel, Rosenbluth and Samet²⁶ reported the presence of P- and T-waves in tracings taken from the anterior chest wall using needle electrodes after they had been absent in the usual leads from the extremities. Leiman, Clark and Means,¹⁶ however, using both needle electrodes and standard contact electrodes in a series of instances, found little change in the tracings.

Before treatment (figure 3) the tracings from our case showed a sinus bradycardia, small P-waves in Leads I and III, prolonged P-R interval (0.22 second), low amplitude of the QRS complexes, small T₁, and small diphasic T₃. After two months of treatment the T-waves had become more pronounced, there was increased amplitude of the QRS complexes, and the rate had increased to 84 per minute. These changes were definite, and although not as striking as some of those reported, they are considered characteristic of "myxedema heart."

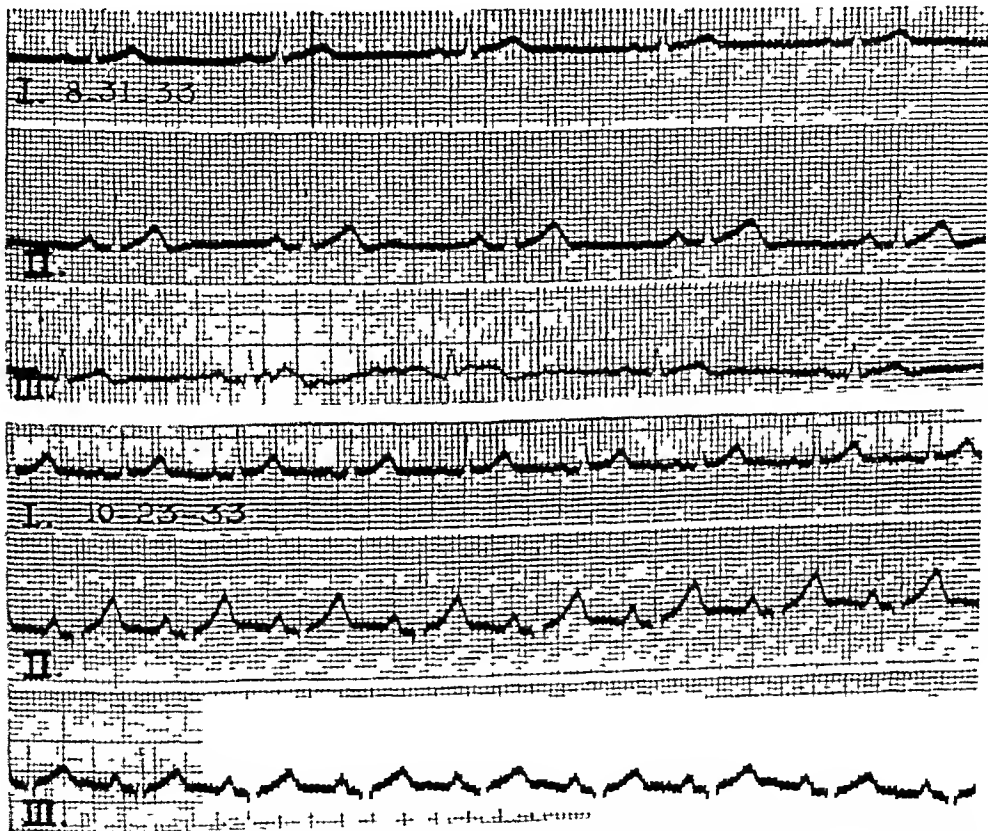


FIG 3 Electrocardiographic tracings showing the following effects of treatment (1) increased rate, (2) increased amplitude of the P-waves, QRS complexes, and T-waves, and (3) decreased P-R interval

After thyroid had been discontinued there was some reversion to the former type with decreased amplitude of the QRS complexes and T-waves, slowing of the rate, and slight prolongation of the P-R interval.

Intestinal Atony Constipation is an almost constant finding in hypothyroidism. Mathers²⁷ demonstrated atony of the colon by roentgen-ray which improved with thyroid-therapy, and Deusch²⁸ showed experimentally that thyroid caused increased intestinal tonus both in experimental animals and in man. Brown^{29, 30} noted the occasional marked improvement in pa-

tients complaining of intractable constipation after thyroid medication and found such patients to have low basal metabolic rates. Wohl³¹ describes the condition as the "lazy bowel of myxedema," and Lisser²⁴ emphasizes its frequency.

The fact that the abdominal complaint of "bloating and gas" is the one that brought our patient to the clinic for medical attention demonstrates the importance to the patient of this phase of the disease. The symptoms were probably partly due to the ascites and partly due to the atonic bowel. It is also noteworthy that a "questionable mass behind the stomach, causing forward displacement," was reported after the first roentgen-ray examination of the gastrointestinal tract. Subsequent examination proved this "mass" to be gas in the distended splenic flexure of the colon.

The findings after barium enema demonstrated clearly the effect of the thyroid-therapy on the colon. Following the enema the patient was told to expel voluntarily as much as she could of the enema material, after which another film was taken. As shown in figure 4, at first very little of the



FIG 4 Colon films taken after voluntary evacuation of the barium enema material. These show obvious increase in tone with resultant improved emptying.

barium was expelled, but after treatment there was a marked improvement in tone and much more of the barium could be expelled voluntarily. It is interesting to note that in spite of this demonstrable improvement in bowel function, there was practically no change in the patient's constipation. However, the bloating, gas, and upper abdominal pain of which she first complained had entirely disappeared after treatment was in progress. This improvement can perhaps be attributed to the increased tone of the small and large intestine. The symptoms leading up to her operation were prob-

ably of a functional nature and not connected with hypothyroidism. However, hypothyroidism as a cause of abdominal pain has been emphasized by Hinton³² and Lissner³⁴.

Anemia Anemia of varying grades is found almost constantly in myxedema of any duration. It is usually secondary in type and in a certain percentage of instances will respond to thyroid medication alone, as in cases reported by Emery,³³ Mackenzie,³⁴ Stone,³⁵ and Lissner and Anderson.¹³ In other cases, as pointed out by Lerman and Means,³⁶ iron is necessary in addition to the thyroid. The occasional similarity of the anemia to pernicious anemia, including the fairly frequent finding of achylia gastrica, has been noted by the above authors, but in the majority of the cases, the blood responds to thyroid, or, thyroid and iron. However, Means, Lerman and Castle,³⁷ and Lissner and Anderson,¹³ have reported patients with coexistent myxedema and pernicious anemia, the latter diagnosis being supported not only by clinical and blood findings, but also by typical reticulocyte responses to liver therapy. In this group, of course, thyroid and liver therapy must be administered simultaneously.

When our patient was first seen, pernicious anemia was considered in the differential diagnosis, but the finding of normal acidity in the gastric juice made this diagnosis improbable. After treatment was started, thyroid alone was given for a period of two and one-half months. During the last two months of this period the metabolic rate was normal and there was marked improvement in most of the symptomatology, but the red blood cells and hemoglobin remained at practically the same level. The patient was then started on iron and ammonium citrate in addition to the thyroid. When she returned to the clinic after an interval of seven weeks, the blood picture had risen almost to normal. The counts were as follows:

	Hemoglobin (Sahli)	Red Blood Cells per cu mm
8-23-33	55 per cent	2,700,000
8-25-33	50 per cent	3,160,000
	Thyroid therapy started—	
10-23-33	55 per cent	2,810,000
11-20-33	45 per cent	2,800,000
	Iron and ammonium citrate started (in addition to thyroid)—	
1-16-34	76 per cent	4,660,000
2-16-34	80 per cent	4,450,000

This classifies the anemia as definitely of the secondary type, and one in which both iron and thyroid were necessary. It seems probable that the long duration of the anemia, as evidenced by the history of a blood test of "60" eight years before, was a factor in necessitating the administration of both iron and thyroid before improvement resulted. The results may also indicate that iron given routinely in conjunction with thyroid will probably result in the more rapid improvement of the secondary anemia of myxedema even though it might eventually respond to thyroid alone. Such a conclusion was reached by Lerman and Means.³⁶

Menorrhagia The possibility of hypothyroidism as a cause for menorrhagia and metrorrhagia was noted by Salzman³⁸ and its frequency stressed by Lissner³⁹⁻⁴¹ and Gardiner-Hill and Smith⁴⁰. A striking case was reported by Lissner and Anderson,⁴³ and a recent article by Waters and Williams⁴¹ contains an excellent review of the literature on this subject. The association is now widely accepted and it is, or should be, common practice to have a determination of the basal metabolic rate in patients where no obvious local pathology can be found to account for uterine bleeding. All authors agree that thyroid-therapy will reduce the bleeding to normal amounts if hypothyroidism is the etiologic factor.

The effect of thyroid-therapy on our patient's menses was marked and characteristic. Her menstrual history prior to treatment revealed that her periods had always been very profuse and lasted seven to eight days. During the year preceding entry they had been irregular, but continued to be profuse, lasting eight to ten days.

After therapy was started, the periods became regular, lasted three to four days, and there was a marked diminution in the amount of flow. This improvement has persisted.

Other Considerations The presence of carotinemia can be explained partially by the patient's dietary habits, but it is obvious, as in most such cases, that normal people could eat a similar diet without developing the pigment retention necessary for increased icterus index and deposition of the pigment in the tissues. It seems logical to conclude that some metabolic change is partially, at least, responsible for the development of carotinemia. Since most patients with myxedema are described as having a yellowish tint, it would be interesting to see how frequently carotin can be detected in their blood serum. It may be that there is an increased incidence in myxedema similar to that noted by Rabinowitch⁴² in diabetes, another disease of disturbed metabolism.

The depressed liver function, as evidenced by the definitely abnormal values in the Rose Bengal liver function test before treatment (specimen I—62 per cent retention, specimen II—44 per cent), is noteworthy, especially since hepatic dysfunction has been noted in hypothyroidism by Rowe⁴³ and Lissner²⁴. The improvement after therapy to within approximately normal limits (I—53 per cent, II—32 per cent) apparently indicates that in this patient thyroid also had an effect on the rate of dye excretion through the liver. Retention was again found to be increased (I—78 per cent, II—60 per cent) after the operation, but how much of this was due to the lack of thyroid and how much due to the anesthetic is impossible to decide. The relation of the pigment retention of carotinemia to decreased liver function is another question for speculation.

Thyroid-therapy also influenced the sugar tolerance curve and the relatively flat curve before treatment was transformed into a curve somewhat similar to that seen in hyperthyroidism. After thyroid had been stopped the curve again became flat. The values are as follows:

Basal Meta- bolic Rate	Blood Sugar— Fasting	30 minutes	60 minutes	120 minutes
Minus 41%	77 mg %	137 mg %	156 mg %	148 mg %
Plus 3%	108 mg %	186 mg %	218 mg %	141 mg %
Minus 22%	82 mg %	—	137 mg %	84 mg %

These results are somewhat similar to those published by Gardiner-Hill, Brett and Smith⁴⁴ in an article on this phase of myxedema

Hypothyroidism vs Myxedema Cases of hypothyroidism without myxedema are not rare King⁴⁵ noted that a low basal metabolism should be suspected in protracted menopause or chronic eczema Lawrence^{46, 47} noted thyroid failure without myxedema in patients whose chief complaints were headache and constipation Higgins⁴⁸ reported similar cases and noted the occasional finding of edema Blumgarten⁴⁹ stressed, in addition, rheumatoid pains and anemia McKean,⁵⁰ Warfield,⁵¹ and Hensel⁵² note the frequency of this syndrome in the goiter region around the Great Lakes but other authors, including Thurmon and Thompson,⁵³ Lissner and Anderson¹³ and, more recently, Youmans and Riven⁵⁴ have reported groups of such cases from regions where goiter is not common All report improvement of the various complaints on thyroid-therapy The various manifestations have recently been catalogued by Lissner²⁴

Clinically our patient did not have typical myxedema, although she did present dry skin, pallor, and scanty, coarse hair However, there was no puffiness of the features, she was not obese, and there were no subcutaneous fat pads Her speech was slow but not otherwise remarkable and mentally she seemed alert The picture was not one to be compared with that of Evans' patient¹ who presented typical far-advanced myxedema and on whom "the nurse made the diagnosis at one glance" It required some investigation before the diagnosis of hypothyroidism became apparent

After considering the paucity of external signs, it is interesting to note the abundance of internal signs brought out by the clinical and laboratory investigations The cardiac, intestinal, and bladder atony, as well as the anemia, were all typical of myxedema Since the external signs were not at all typical, the term "internal myxedema" seems an appropriate designation for the findings in our patient The presence of ascitic fluid makes this descriptive term even more pertinent

SUMMARY

A case of hypothyroidism is reported which showed ascites, cardiac, intestinal and bladder atony, secondary anemia, menorrhagia and associated carotinemia

The ascitic fluid was thought to be due to the hypothyroidism and showed a protein content above the average, but not as high as some previously reported

The cardiac findings were typical of myxedema heart without decompensation

The condition of bladder-atonny is thought to be more common than previously reported

The patient was followed over a period of 13 months and all symptoms and signs showed improvement on thyroid-therapy except the anemia, for the improvement of which iron was necessary in addition to the thyroid

An exploratory laparotomy performed for symptoms simulating partial intestinal obstruction showed no evidence of other etiology for the ascites

It is suggested that the term "internal myxedema" would best describe the findings in this patient

BIBLIOGRAPHY

- 1 EVANS, W Case of myxedema with ascites and atony of urinary bladder, *Endocrinology*, 1932, *xvi*, 409-416
- 2 ALTHAUSEN, T L, BISKIND, G R, and KERR, W J Rose Bengal test of hepatic function, spectroscopic method, *Jr Lab and Clin Med* 1933, *xviii*, 954-958
- 3 MUSSIO FOURNIER, M J C Syndrome hydropigme et insuffisance thyroïdienne *Bull Acad de med, Paris*, 1925 *xiii*, 691-694
- 4 MARSH, H E Myxedematous ascites removed by thyroid extract, *Am Jr Med Sci* 1926, *clxxii*, 585-588
- 5 DAVIDSON, J R Adolescent myxedema accompanied by nephrosis, and in one case, tetany, *Canad Med Assoc Jr*, 1925, *xv*, 598-600 Adolescent myxedema, accompanied by nephrosis and by tetany of parathyroid origin treated with thyroid and Collip's parathyroid extract, *ibid* 1925, *xv*, 803-808 Nephrosis of thyroid origin, *ibid*, 1926, *xvi*, 1059-1063, *ibid*, 1928, *xviii*, 161-164
- 6 BFRTERVIDE, J J, and HERRERA L M Ascitis e insuficiencia tiroidea *Arch argent de enferm d ap digest y de la nutricion* 1932, *xii* 353-358
- 7 EPSTEIN, A A Studies on the chemistry of serous effusions, *Jr Exper Med*, 1914, *xx*, 334-345
- 8 SALVESON, H A and LINDER, G C Inorganic bases and phosphates in relation to the protein of blood and other body fluids in Bright's disease and in heart failure, *Jr Biol Chem*, 1923, *lviii*, 617-634
- 9 FOORD A G, YOUNGBERG, G E and WETMORE V Chemistry and cytology of serous fluids, *Jr Lab and Clin Med*, 1929, *xiv*, 417-428
- 10 MACHEBOEUR, M A, and FETHKE, N Recherches sur les lipides et les proteides des liquides d'epanchements non-purulents des sereuses, *Bull Soc chim biol*, 1932, *xiv*, 507-520
- 11 BRICK H G Association of urologic lesions with hypothyroidism, *Endocrinology*, 1927, *xi*, 438-444
- 12 ZONDER H Das Myxedemherz, *Munchen med Wchnschr*, 1918, *lxv*, 1180-1182
- 13 LISSER H, and ANDERSON, E M Three cases of adult myxedema in women reported for the purpose of calling attention to their widely different symptomatology and clinical findings, *Endocrinology*, 1931, *xv*, 365-381
- 14 AYMAN, D, ROSENBLUM, H, and FALCON-LESSER, M "Myxedema heart" without evidence of cardiac insufficiency, *Jr Am Med Assoc*, 1932 *xcvii*, 1721-1725
- 15 GALLAGHER J R Myxedema heart disease—with report of one case, *Yale Jr Biol and Med*, 1932, *v*, 75-80
- 16 LFRMAN, J CLARK R J, and MEANS, J H Heart in myxedema *ANN INT MED*, 1933, *vi* 1251-1271
- 17 FAHR, G Myxedema heart, *Jr Am Med Assoc*, 1925, *lxxxiv*, 345-349
- 18 CHRISTIAN, H A Heart and its management in myxedema, *Rhode Island Med Jr*, 1925, *viii*, 109-118

- 19 STURGIS, C C, and WHITING W B Treatment and prognosis in myxedema, Jr Am Med Assoc, 1925, lxxxv, 2013-2017
- 20 FISHBERG A M Arteriosclerosis in thyroid deficiency, Jr Am Med Assoc, 1924, lxxxii, 463-464
- 21 DUDEN, C W Myxedema with cardiac decompensation and hypertension which disappeared under thyroid medication, Jr Missouri Med Assoc, 1929, xxxi, 25-27
- 22 THOMPSON, W O, DICKIE, L F N, MORRIS, A E, and HILKOVITCH, B H High incidence of hypertension in toxic goiter and in myxedema, Endocrinology, 1931, xi, 265-272
- 23 THACHER, C, and WHITE, P D Electrocardiogram in myxedema, Am Jr Med Sci 1926, clxxi, 61-66
- 24 LISSER H Clinical indications for proper use of thyroid substance, Internat Clin 1933, iv, 66-101
- 25 FAHR, G Myxedema heart, Am Heart Jr, 1927, iii, 14-30
- 26 NOBEL E, ROSENBLUTH, A, and SAMET B Das Elektrokardiogramm des kindlichen Myxodems, Ztschr f d ges exper Med, 1924, xliii, 332-341
- 27 MATHERS A T A case of myxedema, Canad Med Assoc Jr, 1920, x, 859
- 28 DEUSCH, G Thyroid and motility of intestines, Deutsch Arch f klin Med, 1923, cxlii, 1-31, *Abstr* Jr Am Med Assoc, 1923, lxxxvi, 171
- 29 BROWN T R Hypothyroidism as a cause of intractable constipation Trans Assoc Am Phys, 1926, xli, 162
- 30 BROWN, T R Effect of hypothyroidism on gastric and intestinal function, Jr Am Med Assoc, 1931, xcvi, 511-513
- 31 WOHL M G Hypothyroidism with special reference to gastrointestinal tract, Med Clin N Am, 1931, xiv, 1017-1023
- 32 HINTON, J W Abdominal pain due to hypothyroidism, Jr Am Med Assoc, 1932, xcvi, 1702-1703
- 33 EMERY E S JR Blood in myxedema Am Jr Med Sci 1923, clxi, 577-583
- 34 MACKENZIE, G M Anemia in hypothyroidism, Jr Am Med Assoc, 1926 lxxxvi, 462-464
- 35 STONE C T Occurrence of anemia in myxedema, ANN INT MED 1928, ii, 215-221
- 36 LFRMAN J and MEANS J H Treatment of anemia of myxedema Endocrinology, 1932 xvi, 533-540
- 37 MEANS J H, LFRMAN J, and CASTLE W B Coexistence of myxedema and pernicious anemia, New England Jr Med, 1931, cciv, 243-248
- 38 SALZMAN S Hypothyroidism a factor in certain types of uterine hemorrhage, Am Jr Obst 1916 lxxiv, 812-818
- 39 LISSER H In BLUMER G Bedside diagnosis, 1928 W B Saunders Philadelphia
- 40 GARDINER-HILL H, and SMITH, J F Menorrhagia as symptom of myxedema, Lancet, 1927, i, 862-864
- 41 WATERS W C, JR, and WILLIAMS G A Menorrhagia due to hypothyroidism Am Jr Obst and Gynec, 1932, xxiii 489-493
- 42 RABINOWITCH, I M Carotinemia and diabetes Canad Med Assoc Jr, 1928, xvi, 527-530
- 43 ROWE A W Endocrine studies association of hepatic dysfunction with thyroid failure, Endocrinology, 1933 xii 1-22
- 44 GARDINER-HILL H BRETT P C and SMITH J F Carbohydrate tolerance in myxedema, Quart Jr Med, 1925, xviii, 327-334
- 45 KING, J T, JR Hypothyroidism, Southern Med Jr 1924 xvii, 662-669
- 46 LAWRENCE C H Studies in endocrinology I Hypothyroidism with and without myxedema, Boston Med and Surg Jr, 1924, cxc, 307-312
- 47 LAWRENCE C H Thyroid failure without myxedema, Med Clin N Am, 1925, viii 1779-1788

- 48 HIGGINS, W H Incipient hypothyroidism, clinical study, Jr Am Med Assoc, 1925, lxxxv, 1015-1017
- 49 BLUMGARTEN, A S Unusual forms of hypothyroidism, Med Clin N Am, 1928, xi, 593-602
- 50 MCKEAN, R M Hypothyroidism without myxedema, its recognition and treatment, Jr Michigan Med Soc, 1929, xxviii, 128-131
- 51 WARFIELD, L M Hypothyroidism, Jr Am Med Assoc, 1930, xci, 1076-1080
- 52 HENSEL, C N Non-myxedematous hypothyroidism, Minnesota Med, 1931, xiv, 221-223
- 53 THURMON, F M, and THOMPSON W O Low basal metabolism without myxedema Arch Int Med, 1930 xlii, 879-897
- 54 YOUNG, J B and RIVEN, S S Hypothyroidism without myxedema, ANN INT MED, 1932, v, 1497-1505

RECOVERY FROM CORONARY THROMBOSIS; REPORT OF EIGHT CASES, WITH PARTICULAR REFERENCE TO THE RECOGNITION OF THE LESS SEVERE AND ATYPICAL TYPES¹

By CARTER SMITH, M D , and H CLIFF SAULS, M D , F A C P ,
Atlanta, Georgia

LEVINE¹ in a study of 145 patients with coronary thrombosis found an immediate mortality of 53 per cent Willius and Barnes² are also of the opinion that approximately 50 per cent die in the immediate attack Conner and Holt³ in studying a series of 287 patients with coronary occlusion found an immediate mortality of 16.2 per cent with a subsequent death rate of 55 per cent when averaged over a period of 3 months to 17 years These statistical values are derived almost entirely from those patients who presented the classical clinical picture of coronary thrombosis and undoubtedly include principally those with the more severe grades of the disease Little mention is made of those patients who have occlusions of the smaller coronary vessels and present atypical symptoms of less severity Very few studies are available from which to estimate a mortality rate which includes this important group

The diagnosis of thrombosis of the smaller coronary vessels is much more difficult than that of the classical attacks already so well described in the literature The majority of patients having the less severe grades of the disease are usually diagnosed angina pectoris or "acute indigestion" Most often they are treated with nitroglycerine or with sodium bicarbonate and laxatives and allowed to continue the pursuit of their daily duties In this group sudden death is frequent Had a correct diagnosis been made of the nature of the initial attack, and the patient subjected to a period of four to six weeks of bed rest the fatal event might have been prevented or at least postponed

It is the purpose of this paper to present five patients with the less severe grades of coronary thrombosis who did not manifest the ordinary clinical signs and symptoms of this disease Without careful clinical and electrocardiographic studies these patients would have been diagnosed and treated as individuals with angina pectoris Three patients with severe and unmistakable coronary occlusion are also reported because of their phenomenal recoveries and the serial electrocardiographic studies which they afforded

The character of the pain is of great importance in diagnosing patients with atypical attacks of coronary thrombosis A persistent substernal ache with substernal oppression is much more significant of coronary occlusion than is transient precordial pain The possibility of unusual pain radiation, as has been pointed out by Libman⁴ and others, must also be borne in mind

* Received for publication November 26, 1934

The pain may radiate to the mastoid regions, the shoulders, the elbows, and on some occasions to the abdomen. Occasionally the pain is felt in these remote areas without any conscious radiation from the sternum or left chest. In some instances pain may be entirely absent. Persistent substernal oppression may then be the significant symptom. The usual drop in blood pressure, increase in pulse rate, fever and leukocytosis are often absent in patients having the less severe forms of coronary occlusion. Then the only criterion by which a positive diagnosis may be reached is the demonstration of changes in the form of the T-wave^{*} in electrocardiograms taken over a period of days or weeks.

The electrocardiogram of an individual is a remarkably constant curve unless altered by some pathological change in the myocardium or by the action of one of the digitalis bodies. The pathological events causing a sudden change in the structure of the myocardium are almost entirely limited to some disturbance in the blood supply of the myocardium. The most frequent cause of this is coronary thrombosis. Ischemia of the myocardium may occur as a sudden event and not be due to coronary vessel disease. This is probably best illustrated by large pericardial effusions. In this condition we sometimes see changes in the electrocardiogram similar to those that occur in coronary occlusion.⁵ Katz and Wallace⁶ have pointed out that myocardial ischemia may occur without coronary occlusion or pericardial effusion and produce changes in the electrocardiogram that may be confused with coronary occlusion. This occurred, however, only with advanced cardiac failure.

The demonstration of changes in the form of the T-wave occurring over a period of days or weeks in an individual who clinically suggests the possibility of coronary thrombosis is almost confirmatory evidence of this disease. This change may occur in the first few hours of the disease and disappear in even as short a time. Again it may not occur for several days and in some instances weeks after the accident has occurred.⁶

Individuals who have persistent substernal pain or recurring precordial pain of varying degrees of severity often do not show on one or two observations changes in the electrocardiogram suggestive of coronary thrombosis. If serial records are made over a period of several days, however, we can often demonstrate electrocardiographic changes strongly suggestive of small coronary infarctions. Should such changes be demonstrated the patient should be treated as one with a typical coronary thrombosis even though clinically he presents only the picture of an angina pectoris or less. Proger and Ayman⁵ have shown that nitroglycerine may occasionally precipitate a dangerous lowering of blood pressure and that it should be used with great caution in treating paroxysms of pain in patients with hypertension or generalized vascular disease.

* Reference to the changes that occur in the T-waves includes also any changes that might occur in the S-T segments.

We believe that the early recognition and proper treatment of patients with the smaller and less severe occlusions will considerably reduce the mortality rate of this disease

The following five case reports illustrate the diagnosis and recovery of patients with the less severe grades of coronary thrombosis

CASE REPORTS

Case 1 J P, a 48 year old traveling salesman, was first seen in 1928 with an attack of renal colic. At this time the only complaint referable to the cardiovascular system was slight dyspnea on over-exertion. He had, however, experienced four attacks of "acute indigestion" with sharp pains in the epigastrium during the past four or five years. His blood pressure was at that time 120 mm of mercury systolic and 70 mm diastolic. There was no enlargement of the heart. The heart sounds were of normal quality. There was an early generalized arteriosclerosis.

Two years later the patient was seen complaining of a dull substernal ache on exertion. He also experienced a sense of oppression beneath the sternum. The blood pressure was 140 mm systolic and 80 mm diastolic. There was no significant change found on physical examination except an arrhythmia, due to premature auricular beats. The first sound at the apex was of fair quality and there was no enlargement of the heart. An electrocardiogram at that time (figure 1) showed evidence of myocardial disease but was not particularly suggestive of coronary disease. In the light of the previous attacks of epigastric pain associated with "indigestion" and the recent substernal oppression we suspected coronary disease and advised him to remain in bed for a period of at least four weeks. His symptoms rapidly subsided and at the end of this time he felt quite well and was allowed to return to part time work.

Comment This patient did not at any time present symptoms sufficient to warrant a diagnosis of coronary thrombosis. The persistent substernal aching and sense of oppression were suggestive of coronary vessel disease and the changes that occurred between his first and second electrocardiogram made during an interval of one week justified a suspicion of coronary occlusion. The T-waves were inverted in all leads and associated with an S-T deviation from the base line. In the second record, seven days later, the T-waves were becoming upright. In the subsequent records made during the next 15 months the T-waves became completely upright in Leads I and II. We interpreted this change in the form of the electrocardiogram as indicating a small coronary occlusion, not sufficiently severe to produce clinical signs and symptoms of coronary thrombosis but involving enough of the myocardium to produce changes in the electrocardiogram.

Case 2 Mrs W S, a 47 year old housewife, was first seen on May 20, 1931, complaining of indigestion, precordial pain radiating down both arms, and nervousness. Three years before she first noticed palpitation and shortness of breath on exertion. One year ago she consulted a physician because of "indigestion". She was found at that time to have a blood pressure of 185 mm systolic and 100 mm diastolic. During the past two years she has had occasional attacks of substernal pain which radiated to the shoulders and down both arms. The attacks gradually became more frequent and severe. Any emotional upset or exercise would precipitate

No 1
Mr J P
age 48

*Moderate Generalized Arteriosclerosis
Coronary Occlusion*

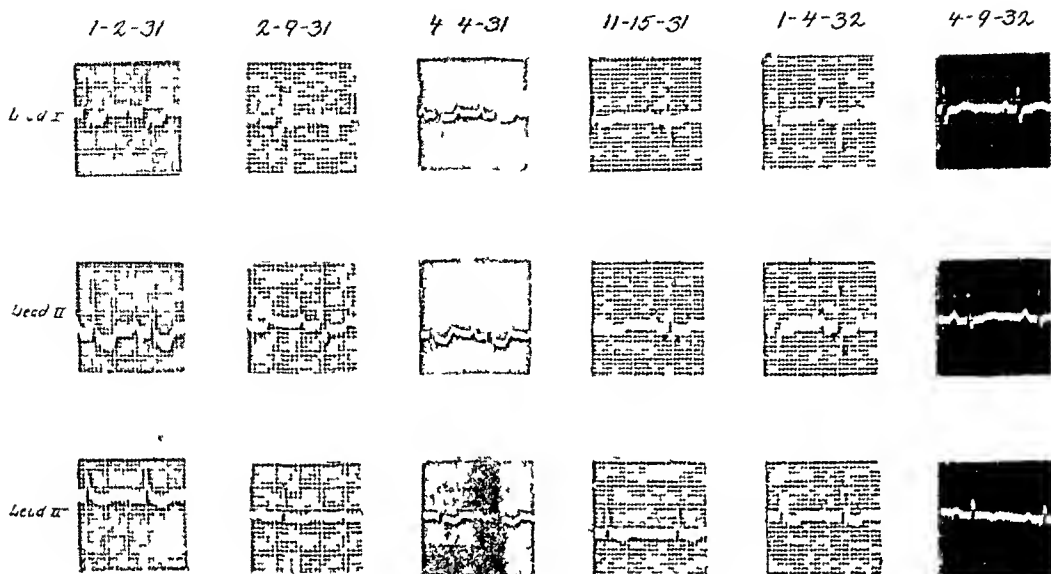


FIG 1 J P

1-2-31 Substernal oppression and mild precordial pain first noticed a few days before this record was made. The T-waves are inverted in all leads. Slight depression of the S-T interval in Leads I and II. Slight elevation of the S-T take-off in Lead III.

2-9-31 After five weeks of rest in bed. Still notices occasional sense of oppression in the chest but no pain. The T-waves in all leads are tending to become upright.

4-4-31 Working as a traveling salesman. Notices only occasional twinge of precordial pain and some fullness in the epigastrium. The T-waves of Lead I have become upright.

11-15-31, 1-4-32, 4-9-32 Is symptom-free and working without difficulty. The T-waves of Leads I and II have finally become upright while the T-waves of Lead III are isoelectric.

an attack. The patient's family history was of interest in that she had a brother who experienced attacks of precordial pain and had an elevated blood pressure.

Physical examination showed a moderately obese, over-active, "high tension" woman of about 45 years. Her weight was 145 pounds. Her height was 63 inches. There was a moderate sclerosis of the temporal, radial and retinal vessels. There was a slight increase in the anteroposterior diameter of the chest. The heart was slightly enlarged. The first sound at the apex was of poor quality. The rate was 100 per minute. The rhythm was regular. The blood pressure was 165 mm systolic and 95 mm diastolic. Laboratory examinations gave normal results except for a questionable trace of sugar in the urine. There was some retention of tetradol in the gall-bladder dye test.

Because of the frequency and severity of the substernal pain the patient was admitted to the hospital. After two weeks of complete bed rest in the hospital the pain became less frequent and less severe. She was discharged to remain in bed at home for four or five weeks longer. At the end of this time the attacks of pain were much less and she was allowed light physical exercise. This was gradually increased.

110 2

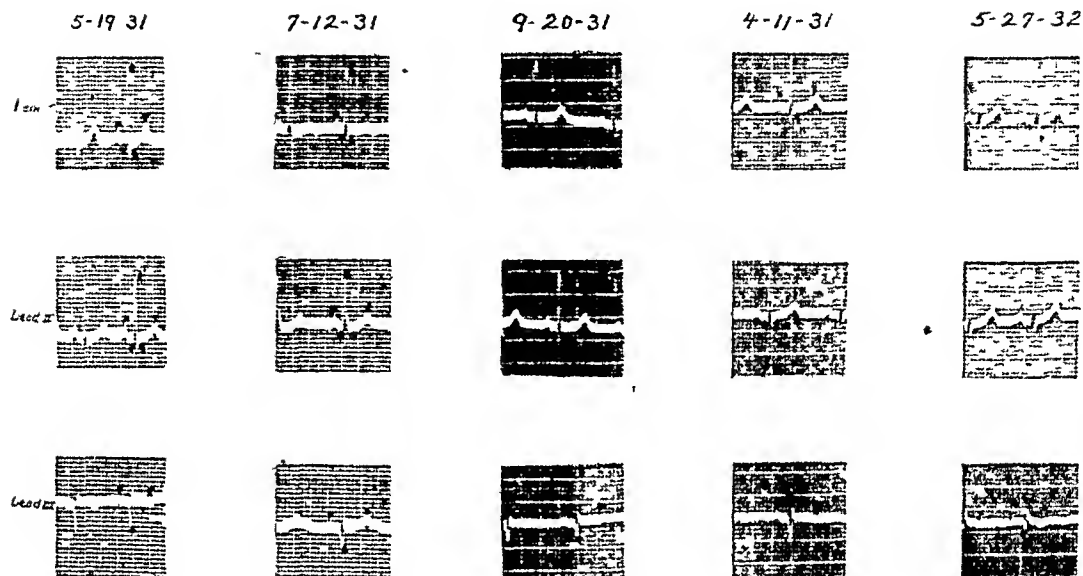
Mrs W S
age 47*Moderate Generalized Arteriosclerosis
Hypertension
Angina Pectoris
Menopause
Obesity*

FIG 2 Mrs W S

5-19-31 Attacks of precordial pain on exertion or emotional upset for the past two years. More frequent and severe lately. In Lead III the 'S' waves are deep and the T-waves are inverted.

7-12-31 After one month of bed rest the attacks of precordial pain have become less frequent. The T-waves of Lead I have become isoelectric and the T-waves of Lead III upright.

9-20-31, 4-11-31, 5-27-32 Moderate physical activity without discomfort. Very occasional attack of pain if emotionally upset or just preceding menses. The T-waves of Lead I have become upright and remained so throughout the remainder of the time she was observed. The T-waves of Lead III have again become inverted.

until she could, without discomfort, perform moderate physical exercise. There was an occasional recurrence of the attacks of precordial pain if the patient became emotionally upset and before the onset of her menstrual periods. The patient's weight was gradually reduced to her normal standard and her blood pressure gradually dropped from 165 mm systolic and 95 mm diastolic to 115 mm systolic and 80 mm diastolic.

Comment This patient is quite typical of the individual usually labeled angina pectoris. Coronary thrombosis is seldom suspected until the fatal infarction occurs. The first electrocardiogram, made at the time of her admission to the hospital, showed no evidence of coronary infarction and very little evidence of myocardial disease. The second record, however, made after seven weeks of complete bed rest, showed very definite change in the form of the T-wave in Leads I and III. In Lead I the T-wave had definitely decreased its voltage and was almost biphasic. In Lead III the

T-wave which was inverted in the first record made, had become upright. No digitalis had been given at any time. Subsequent records made at irregular intervals during the next 10 months showed a return of the T-wave in Lead I to its upright position and the T-wave of Lead III once more became inverted.

These changes are difficult to interpret as a definite coronary thrombosis. The evidence, however, is strongly suggestive that some acute pathological changes occurred in the myocardium. This, in the light of the clinical history and physical examination, was probably associated with pathologic changes in the coronary vessels and it is difficult to conceive that a coronary spasm would be capable of producing such changes in the electrocardiogram over a period of 12 months. To treat such patients for coronary thrombosis is at least a safer procedure than to give nitroglycerine and allow them continued physical activity.

Case 3 Mrs. V. H., a 50 year old housewife, was admitted to the hospital July 6, 1931, complaining of pain over the lower part of the sternum which radiated up both sides of the neck. Five months before, while walking she experienced a sensation of oppression in her chest and some precordial pain. This discomfort occurred only when she exercised, and disappeared on resting. During the past month the attacks of precordial pain have occurred almost every day and even while at rest. The radiation has extended down the left arm. She has also experienced considerable gas and fullness in the epigastrium after meals. The family history was of importance in that her mother died at the age of 60 with apoplexy.

On physical examination she was moderately obese. There was evidence of a moderate generalized arteriosclerosis and of slight cardiac hypertrophy. The blood pressure was 130 mm. systolic and 75 mm. diastolic. The heart sounds were of fair quality. There was a soft systolic murmur at the apex. There was slight tenderness in the epigastrium.

Laboratory examinations, which included a gastrointestinal series and gall-bladder tests, showed nothing abnormal. A roentgen-ray of the lumbar spine showed a moderate hypertrophic arthritis.

During the five weeks' stay in the hospital the precordial pain became much less and she was generally improved. After leaving the hospital she remained in bed at home for four weeks. Light physical activity was then begun and gradually increased to moderate activity without difficulty. The attacks of precordial pain disappeared entirely and when last heard from seven months after her stay in the hospital she was complaining only of aching joints.

Comment As in the preceding case report the clinical evidence of a coronary thrombosis is definitely lacking. The most obvious clinical diagnosis was angina pectoris. It is difficult, however, to conceive of such changes occurring in the electrocardiogram without definite pathological changes occurring in the myocardium. We are interpreting these changes in the T-wave and the S-T interval as evidence of a small coronary vessel thrombosis.

Case 4 Mrs. W. B. H., a 58 year old housewife, was first seen 10 years ago complaining of indigestion and nervousness. At that time she had slight dyspnea and

703
Mrs V H
Age 58

Moderate Generalized Arteriosclerosis
Angina Pectoris
Coronary Occlusion
Chr Hypertrophic Arthritis

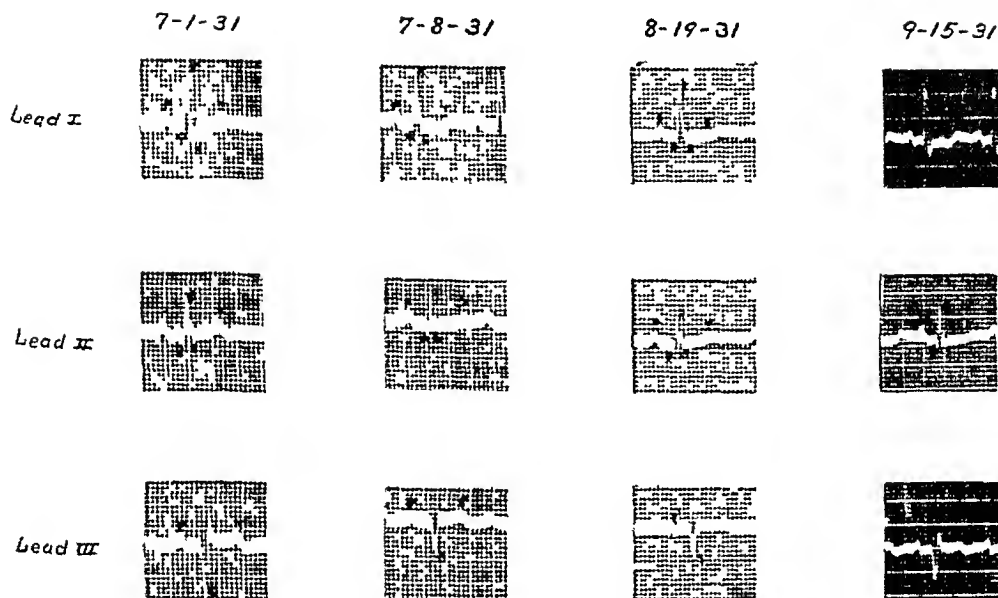


FIG 3 Mrs V H

7-1-31 Moderately severe attacks of precordial pain on exertion, and occasionally while resting, for several weeks. The S-T take-off is slightly below base line in Lead I and slightly below in Lead III.

7-8-31 After two days' complete bed rest, still having mild attacks of precordial pain. The T-waves of Lead I have become inverted and remained so during the remainder of our study. The T-waves of Lead II have decreased their voltage.

8-19-31 After about six weeks of bed rest attacks of pain are quite infrequent.

9-15-31 No more precordial pain. Complains only of pains in her joints.

palpitation of the heart on exertion. She also stated that for years she had experienced attacks of soreness in the upper left abdomen, usually after exertion.

Physical examination at this time showed a moderate generalized vascular disease. Her blood pressure was 140 mm systolic and 90 mm diastolic. The heart was slightly enlarged, measuring 10 cm to the left. She was about 40 pounds overweight. Her blood and urine examinations at this time were normal. A gastrointestinal series showed nothing unusual.

February 11, 1932, ten years after her first visit, she consulted us complaining of a dull substernal pain with radiation to both mastoid regions. This had occurred one week before while climbing a flight of stairs. The substernal pain lasted intermittently for two or three days and then disappeared to return again two days later. It was intermittently present from then until her office visit. It was made worse by physical exercise or emotional upsets.

On examination she was obese. There was moderate general vascular disease. The heart was slightly enlarged. The heart rate was 74 and the rhythm was regular. The sounds were of fair quality. There were no significant murmurs. The blood pressure was 150 mm systolic and 90 mm diastolic. There was no evidence of circulatory incompetence. The temperature was normal and she was in no great discomfort.

An electrocardiogram made at this time (figure 4) showed evidence of definite myocardial disease but was not particularly suggestive of a coronary lesion

We advised a prolonged period of bed rest and this was carried out for six weeks. The pain and substernal discomfort became considerably less, occurring only at infrequent intervals when emotionally disturbed. At the end of six weeks she was allowed light physical activity and this was gradually increased to moderate physical

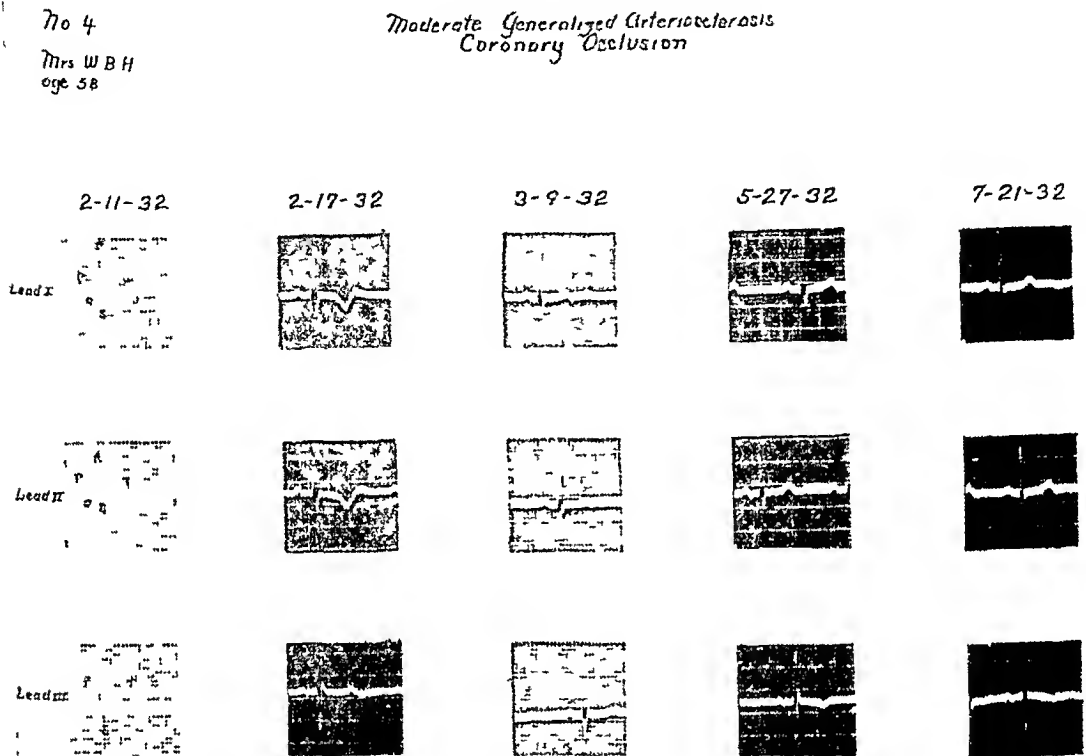


FIG 4 Mrs W B H

2-11-32 Two days after experiencing substernal oppression and aching while walking up steps. No actual precordial pain. No definite clinical evidence of a coronary occlusion. The T-waves of Leads I and II show sharp inversion.

2-17-32 After six days' bed rest slight substernal aching and oppression are still experienced. The sharply inverted T-waves of Leads I and II are unchanged.

3-9-32 After one month of bed rest. Substernal oppression experienced occasionally if emotionally upset. The T-waves of Leads I and II are becoming upright.

5-27-32, 7-21-32 The patient is capable of light physical exercise without discomfort. Occasional attack of mild substernal oppression. The T-waves of Leads I and II have become completely upright. In Lead III they have become inverted. There is very little evidence of pathology in these last records.

activity which she could perform without great difficulty. She still occasionally complains of substernal discomfort if emotionally upset or if she undertakes more than moderate physical exercise. During the period of bed rest there were no essential changes in blood pressure or elevation of temperature, and no leukocytosis.

Comment An electrocardiogram made after one week of bed rest was almost identical with the first record. A third electrocardiogram made after four weeks of bed rest showed a change in the form of T-waves in

Leads I and II The sharp inversion in Leads I and II was beginning to become upright. Subsequent records made at intervals of three and five months after the first observation showed a complete return of the T-waves in Leads I and II to their normal upright position. The T-wave in Lead III became inverted but otherwise the record appeared perfectly normal.

Here again the clinical evidence of coronary thrombosis was lacking. A consideration of this patient's clinical course, together with the changes that occurred in her electrocardiogram over a period of four weeks, makes one suspect strongly an occlusion of a coronary vessel, which did not present typical signs and symptoms of this disease.

Case 5 Mr C C, a hard working high tensioned, traveling salesman of 50 years, was first seen in the office one week after having been seized with a moderately severe attack of pain in the left chest while driving his car. He stopped at the next town and consulted a physician who gave him some tablets which relieved his pain.

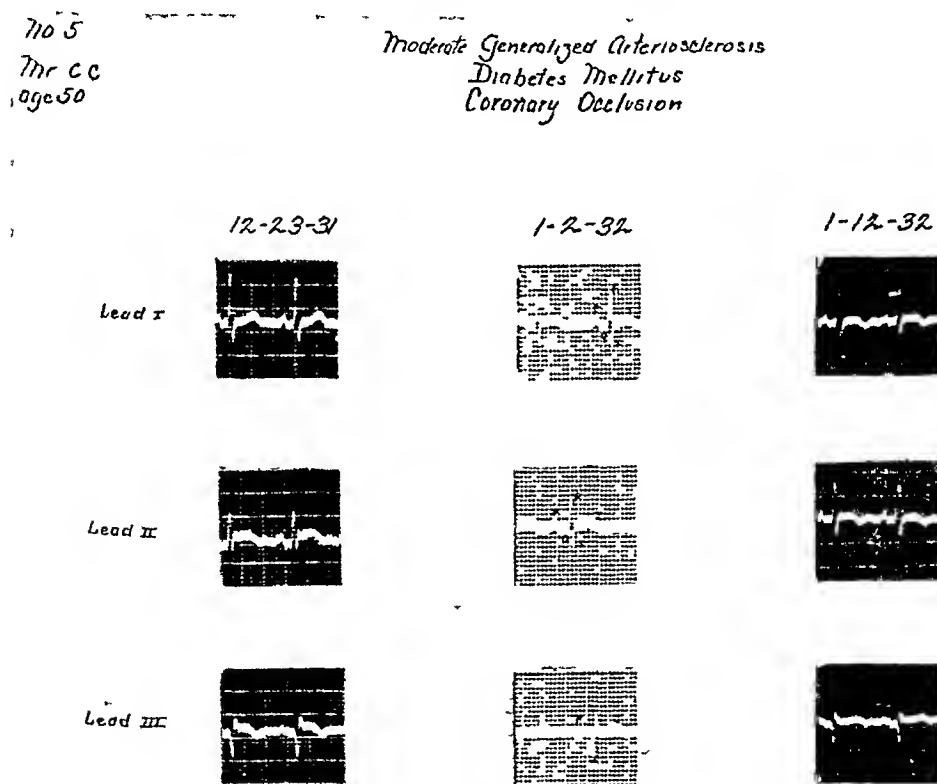


FIG 5 Mr C C

12-23-31 Three days after several attacks of precordial pain of moderate severity. Slight elevation of the S-T interval in Leads II and III. The T-waves of Lead III are inverted.

1-2-32 After 10 days of complete bed rest. No further precordial pain. The T-waves of Lead I have decreased their voltage. The T-waves of Lead III have become upright.

1-12-32 After three weeks of bed rest. The T-waves of Leads I and II have become definitely inverted. The S-T interval in Leads I and II has become dome shaped. Over our protest the patient resumed his duties as a traveling salesman and has had no further precordial pain.

He continued his trip but that night there was a recurrence of the pain. The following day he felt quite well. Four days later he again experienced a constant, dull, non-radiating pain in the precordial region. He consulted another physician who told him that he had diabetes mellitus and neuritis. He visited our office one week after the initial precordial pain.

Physical examination at this time showed the patient to be in no great discomfort. He was of the short, stocky, plethoric type. There was a moderately advanced arteriosclerosis of the peripheral vessels. The tonsils were chronically infected. Chest examination was not abnormal. The apex impulse of the heart was not visible or palpable. The heart was not enlarged. The first sound at the apex was distant. There was a short, soft systolic blow. The heart rate was 100 per minute. The rhythm was regular. The blood pressure was 115 mm systolic and 70 mm diastolic. There was no edema, cyanosis or any other evidence of circulatory failure. His temperature was 100.4° F.

A leukocyte count was 10,000 with 74 per cent polymorphonuclears. Examination of the urine was positive for sugar, acetone and diacetic acid. A fasting blood sugar was 175 mg per 100 cc. An electrocardiogram showed an elevation of the S-T segment in Leads II and III, an inversion of the T-wave in Lead III and a prominent Q₃. The patient was advised a period of complete bed rest, a diet was outlined and 10 units of insulin were given twice daily. No more attacks of precordial pain were experienced after going to bed. In a second electrocardiogram made one week later the T-waves in Lead III had become upright and in Lead II it was becoming biphasic. A third electrocardiogram made three weeks after the onset showed inversion to have occurred in I₁ and T₁ with some rounding of the S-T segment in these leads. After three weeks of bed rest the patient then insisted upon taking up his duties as a traveling salesman. Two years have elapsed since this time and there has been no recurrence of the precordial or substernal discomfort.

The patient has not been seen since the last electrocardiogram was made but inquiries reveal that he is carrying on his usual work without discomfort.

Comment This patient is one of the group that is often classified as angina pectoris. He also illustrates the not infrequent association of coronary disease and diabetes mellitus. His coronary thrombosis in all probability involved only a small vessel as there were very few of the usual signs of this disease.

The following three cases presented no diagnostic difficulties, the clinical features of coronary thrombosis were such as could be diagnosed even without the aid of the electrocardiogram. They are reported because of their interesting recoveries and the data afforded by the serial electrocardiograms. They illustrate the recovery of patients with the more severe lesions and their return to a moderate degree of usefulness.

Case 6 Mr. H. B., a rather high tensioned business man of 57 years who had been a known hypertensive for five years, was first seen at home on January 29, 1932. The day before, while having some dental work done, he first noticed slight substernal pain. A few hours later the substernal pain became more excruciating. He was nauseated and vomited. Shortly after vomiting, the pain subsided and he was comfortable for several hours. About two o'clock the next morning he was awakened with excruciating precordial pain, substernal oppression and breathlessness.

On physical examination at this time he was pale and cyanotic. His respirations were of the Cheyne-Stokes type and his blood pressure had dropped from its usual level of 190 mm systolic and 100 mm diastolic to 100 mm systolic and 70 mm

diastolic The heart was slightly enlarged The sounds were distant and there was a light pericardial friction rub The heart rate was 120 and the rhythm grossly irregular A leukocyte count was 18,600 with 80 per cent polymorphonuclear leukocytes

For the next 10 days the patient's clinical course was quite stormy Hiccoughs and abdominal distention were very severe Auricular fibrillation was paroxysmal and for several days the degree of circulatory shock was marked His temperature elevation fluctuated from 99 to 101 degrees for one week After 10 days the patient's general condition was considerably improved and after remaining in the hospital for four weeks he was transferred home to remain in bed for six more weeks Ten

7106
Mr H B
age 57

*Moderate Generalized Atherosclerosis
Hypertension
Coronary Occlusion*

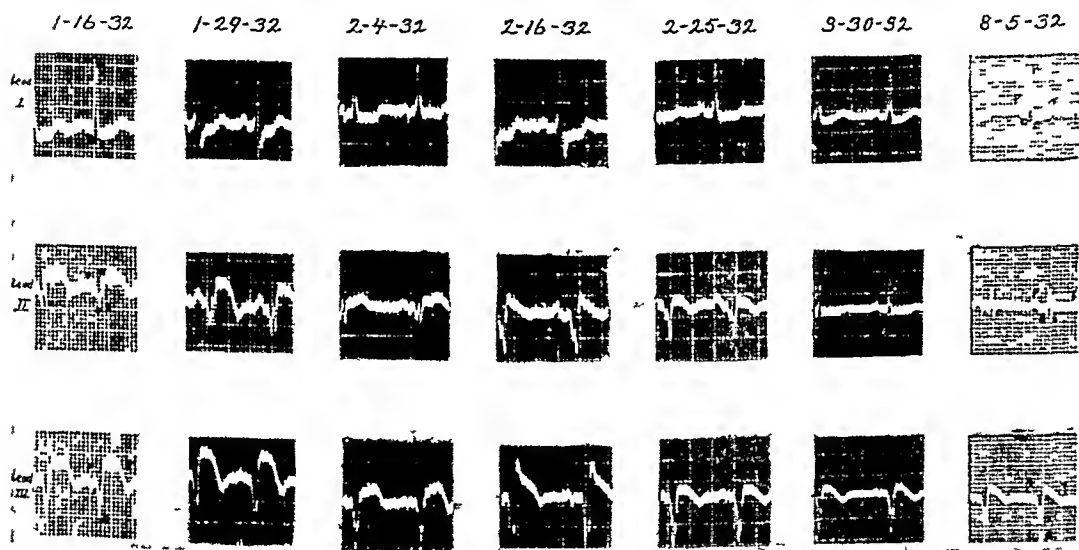


FIG 6 Mr H B

1-16-32 Eight hours after a severe coronary occlusion The S-T interval of Leads II and III shows a marked elevation of the S-T take-off

The subsequent records show the successive changes that occurred in the T-waves as healing progressed At present he is capable of performing moderate exercise

weeks after the occlusion light physical activity was first begun This was gradually increased during the next four months and since then he has been able to participate in moderate physical activities His blood pressure has remained at a lowered level of around 130 mm systolic and 90 mm diastolic The heart rhythm is regular except for occasional ventricular premature beats For several months after the occlusion the patient would experience rather frequent attacks of substernal oppression and soreness This has gradually decreased and at the present time he experiences only occasional sensations of palpitation with the ventricular premature beats Nine months after the coronary accident the patient had influenza and pneumonia No cardiac complications occurred during this illness and his recovery was uneventful Two years have now elapsed since the coronary occlusion He is

capable of performing moderate physical exercise and he seldom experiences any symptoms referable to the heart *

Comment This patient illustrates the more severe grade of coronary thrombosis. The complication of auricular fibrillation presented a problem in therapy as to whether or not digitalis should be used. To leave the ventricular rate extremely rapid and its rhythm irregular, or to risk the possible dangers of digitalis effect on the infarcted myocardium was the question. We elected to use digitalis in an effort to control the heart rate. There were no untoward results from this and as healing began the auricular fibrillation spontaneously disappeared. The patient also presented intractable hiccough. This too disappeared spontaneously.

The first electrocardiogram made about eight hours after the initial coronary occlusion showed a depression of the S-T interval in Lead I and a marked elevation of the S-T interval in Leads II and III. The second record made three days later showed an exaggeration of these findings. A record made 19 days after the thrombosis had occurred showed a beginning return of the S-T take-off to the base line. During the subsequent months an inversion of the T-wave in Leads II and III occurred and the S-T take-off gradually returned toward the base line.

Even though this patient's infarcted area was very extensive his recovery has been quite satisfactory and he is now capable of performing moderate physical activity.

Case 7 Dr. J. T., a 45 year old, sthenic, hard working practitioner, was first seen June 16, 1931. He had been a known hypertensive for 20 years. Three days before, while driving some stakes in his back yard, he experienced pain in both elbows. The next day while driving his car he was seized with a moderately severe precordial pain. He stopped for a few minutes and the pain became less. A few hours later he consulted us in the office.

On examination at this time the patient was in no great discomfort. There was no evidence of circulatory failure or cyanosis. There were moderate generalized vascular changes. The heart was slightly enlarged. The first sound at the apex was of good quality. No murmurs were heard. His blood pressure was 150 mm systolic and 90 mm diastolic. He stated that his average blood pressure was around 180 mm systolic and 100 mm diastolic. The heart rate was 90, and the rhythm was regular. His temperature was 99 degrees. He was about 40 pounds overweight.

An electrocardiogram made at this time showed a very low voltage and inverted T-wave in Lead I. The T-wave in Lead II was also of low voltage and biphasic. There was a left axis deviation.

The patient was advised to go to bed at once. Instead he went to a hospital and performed a laparotomy. Shortly after this he collapsed with acute precordial pain. He was seen a few hours later at home acutely ill with moderate circulatory collapse. His blood pressure had dropped to 115 mm systolic and 70 mm diastolic. The heart rate was 130 and his rhythm was regular. The heart sounds were quite indistinct. The temperature was 101 degrees. A leukocyte count was 14,600 with 68 per cent polymorphonuclear leukocytes. Examination of the urine showed nothing abnormal.

For the following two weeks the patient was quite ill. A pericardial friction rub was heard 48 hours after the acute occlusion. The temperature elevation continued.

* This patient died of congestive heart failure in May 1934, twenty-nine months after his coronary thrombosis.

from 100 to 101 degrees for 10 days. After this time the precordial pain subsided. The convalescence was uneventful. He remained in bed for eight weeks and then for a period of two weeks he participated in light physical activities. Ten weeks after the acute occlusion the patient resumed his practice and since that time he has had only very occasional slight attacks of substernal discomfort. Two and one-half years have now elapsed since the coronary thrombosis and he still feels quite well. In spite of our warning he is working quite as hard as he did before the coronary accident.

No 7
Dr J T
age 45

*Moderate Generalized Arteriosclerosis
Hypertension
Coronary Occlusion*

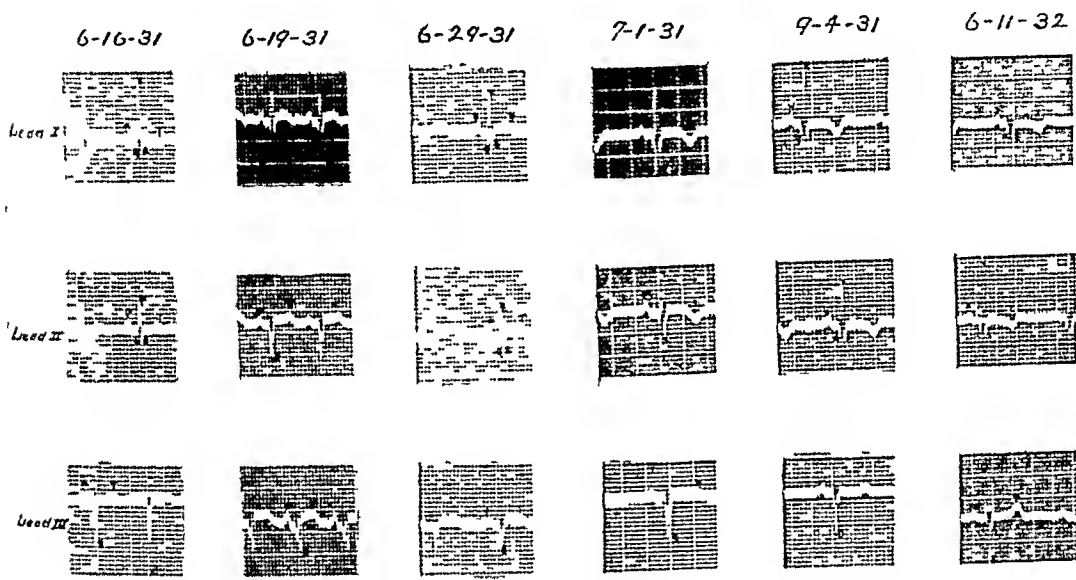


FIG 7 Dr J T

6-16-31 Forty-eight hours after a mild attack of precordial pain. The T-waves of Lead I are inverted and the T-waves of Lead II are biphasic.

6-19-31 Twenty-four hours after a second and very severe attack of precordial pain. Clinically he then presented a typical picture of coronary occlusion.

The subsequent records show the changes that occurred in the T-waves and the S-T intervals during the process of healing. On 6-11-32 he was performing his duties as a general practitioner without difficulty.

Comment From the clinical course it seems that this patient's coronary thrombosis began about 72 hours before his final collapse. It is not improbable to suppose that it began either as a partial occlusion of one of the larger vessels or a complete occlusion of one of the smaller vessels. With continued physical activity the thrombosis became more extensive until it completely shut off one of the larger vessels. Then circulatory collapse ensued. It is of interest to speculate as to whether or not the lesion would have progressed to the severe grade had the patient gone to bed at the time his first symptoms were manifested.

The electrocardiograms taken over a period of one year after the acute occlusion show interesting changes. The record made before the coronary occlusion became complete showed only a slight inversion of the T-wave in Lead I. Three days later, and about four hours after the occlusion became complete, an elevation of the S-T take-off in Leads I and III was first detected. There was also a considerable increase in the shattering of Q-R-S. Two weeks after the complete occlusion the S-T interval was still elevated in its take-off and was beginning to assume the dome shape seen in healing coronary occlusion. Subsequent records made during the next 11 months show the T-waves assuming a sharp inversion in Leads I and II and a return of S-T take-off to its isoelectric level.

This patient again illustrates that the infarcted area can be quite extensive and the patient still recover sufficiently to engage in a useful occupation.

Case 8 M^r. T. S., a 63 year old night watchman, was seen first at 2 a.m., January 6, 1932. A few minutes before, while walking up a flight of stairs, he had been suddenly seized with excruciating pain in the left chest and behind the sternum. When seen he was in a rather advanced state of shock. His color was ashen, perspiration was profuse and the radial pulses were weak and thready. His blood pressure was 80 mm. systolic and 60 mm. diastolic. His heart rate was 120 and regular. There was moderately generalized vascular sclerosis. The heart was not definitely enlarged. The first sound at the apex was quite distant and of poor quality. There was no evidence of pulmonary congestion and the liver was not felt.

The patient was immediately hospitalized. Morphine in one-half grain doses was given and repeated at three hour intervals in order to control the pain.

His "post-thrombosis" course was quite stormy. The temperature ranged from 100 to 101°, his heart rate from 100 to 120 and he had considerable abdominal distention. He had some hiccough and in spite of large doses of morphine his pain persisted for two or three days.

After three or four days his general condition improved. His blood pressure increased to 120 mm. systolic and 90 mm. diastolic. The pain disappeared and his recovery was uneventful. He remained in bed two months. Since then he has gradually increased his exercise until at the present time he is capable of performing light work without discomfort.

Comment An electrocardiogram made 10 hours after the coronary thrombosis shows very little evidence of the accident. This illustrates well that even with an extensive coronary occlusion the changes in the electrocardiogram may not be demonstrable for several hours or even days after the occlusion. In the electrocardiogram made three days after the occlusion only an inversion of the T-wave in Lead III had occurred. Subsequent records made at intervals of three weeks and six months showed an inversion of the T-wave in Leads I and II.

Even though this patient had a moderately advanced generalized vascular disease and an extensive coronary occlusion his recovery has been rather complete in that he does not experience any symptoms referable to the heart even when performing light physical exercise.

No 8
Mr T S
age 63

*Moderate Generalized Arteriosclerosis
Coronary Occlusion*

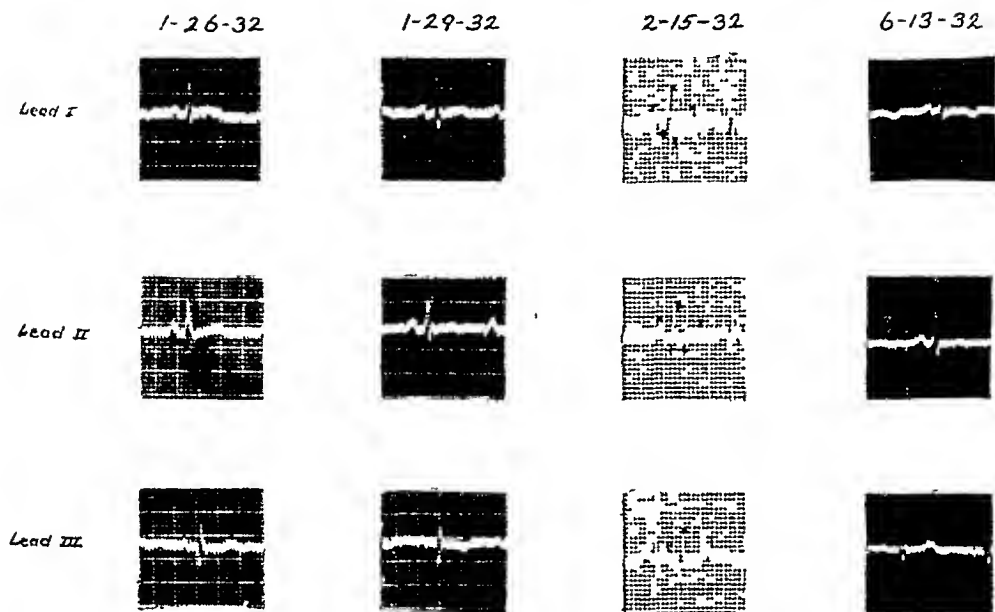


FIG 8 T S

1-26-32 Twenty-four hours after an attack of prostrating precordial pain. The T-waves show no evidence of coronary occlusion. Q- and U-waves in Lead III are suggestive of coronary occlusion. Clinically the patient had a typical attack of coronary occlusion.

1-29-32 Four days after the onset. The T-waves of Lead III have become inverted. The T-waves of Leads I and II still show no evidence of occlusion.

2-15-32 Twenty days after the occlusion. The S-T interval of Lead I has become definitely dome shaped and the T-waves of Lead I have become inverted. The T-waves of Lead II have become upright.

6-13-32 About six months after the coronary occlusion the T-waves in Lead I remain inverted. The patient can perform moderate physical activity without discomfort.

GENERAL DISCUSSION

Death from coronary thrombosis is usually caused by ventricular fibrillation, a rupture of the infarcted area or the throwing off of an embolus. Complete rest offers the best possibility of avoiding these complications. An early diagnosis and the strict enforcement of complete rest are probably the most important factors in the treatment of this disease. The first 21 days after coronary thrombosis constitute the critical period of this illness. If this is passed without complications healing will usually take place and the infarcted area will begin to fibrose. If the infarcted area is not too extensive the heart muscle will remain perfectly competent. As sequelae of large healed infarctions, cardiac hypertrophy and failure sometimes occur during the subsequent months.

The diagnosis of the more severe grades of coronary thrombosis is as a rule not difficult as they usually present the classical syndrome already so well described in the literature. The less severe occlusions that do not manifest typical symptoms of this disease offer an extremely evasive diagnostic problem. They are most frequently diagnosed angina pectoris or some intra-abdominal disease. A correct diagnosis can be made only by the electrocardiographic demonstration of changes in the form of the T-wave in successive records. This diagnostic change may occur within a few hours or not for several days. One or two normal electrocardiograms are consequently of no value in excluding a coronary occlusion.

In order properly to evaluate changes that occur in successive electrocardiograms the technic of making the record must be faultless. Artefacts from faulty connections, high skin resistance and loose strings may cause error to creep into our interpretation. The effect of digitalis or one of its allies must be borne in mind as a factor that may alter the form of the T-wave. Excluding technical error and the effect of drugs, any change in the form of the T-wave of a "coronary suspect" must be regarded as indicative of a coronary thrombosis.

Once the diagnosis is established treatment resolves itself into complete rest for six to eight weeks. Morphine should be used liberally to control the pain and insure complete quiet. Inhalations of oxygen by nasal catheter should be given continuously during the shock stage. Metaphyllin in 0.3 gram doses intravenously is also of value in relieving the pain of the immediate attack.⁹ It may also increase the coronary blood flow and accelerate healing when given by mouth three times daily in 1.5 gram doses. Levine⁹ has suggested the prophylactic use of quinidine sulphate in doses of 4.5 grams three times a day during the 21 day critical period after coronary thrombosis in order to prevent the possibility of ventricular fibrillation. Digitalis is of no value unless cardiac failure or auricular fibrillation is a complication.

After the six to eight week period of bed rest convalescence should be very gradual. The patient should be reeducated as to his mode of living and his occupation. Avoidance of unnecessary physical or mental strains is an essential.

If an electrocardiogram is not available it is much the wiser plan to treat a patient with angina pectoris as one with coronary thrombosis than to treat one with coronary thrombosis as angina pectoris.

Through voluminous publications on this subject the medical profession is quite well instructed as to the diagnosis and treatment of the usual patient with coronary thrombosis. The purpose of this paper is to call attention to those patients who have a thrombosis of the smaller coronary vessels and who do not present the usual classical signs and symptoms of this disease. By the proper diagnosis and treatment of this group we believe the mortality of this disease may be reduced.

SUMMARY

1 We have presented eight patients who have recovered from coronary thrombosis

2 Five of these did not manifest the usual clinical signs and symptoms of coronary thrombosis and ordinarily would have been diagnosed angina pectoris

3 By careful clinical study and serial electrocardiographic tracings taken over a period of days or weeks the diagnosis of coronary thrombosis was established in these patients not presenting the typical signs and symptoms

4 We believe that the immediate mortality from coronary thrombosis may be materially reduced by the early diagnosis and treatment of patients who fail to manifest the usual signs and symptoms of this disease

FOLLOW-UP NOTE

No deaths have yet occurred in the first five patients having the milder attacks of coronary occlusion. From 33 to 46 months have elapsed since their initial attacks. A second attack occurred in one (case 1) 25 months after the first attack. He made an uneventful recovery from this and is now working and without symptoms. All other patients in this group are capable of carrying on their daily duties.

Of the three patients having the severe coronary occlusions, one (case 6) died 29 months after the initial attack with congestive heart failure. Another (case 8) is living and is in fair health, and the third patient (case 7) is without symptoms and doing a large general medical practice 40 months after the initial attack.

BIBLIOGRAPHY

- 1 LEVINE, S. A. Coronary thrombosis, its various clinical features, *Medicine*, 1929, viii, 245-418.
- 2 WILLIUS, F. A., and BARNES, A. R. Recovery after cardiac infarction, *Med Clin N Am*, 1931, xv, 69-77.
- 3 CONNER, L. A. and HOLT, E. Subsequent course and prognosis in coronary thrombosis, analysis of 287 cases, *Am Heart Jr*, 1930, v, 705-719.
- 4 LIBMAN, E. Studies in pain, *Trans Assoc Am Phys*, 1929, xiv, 52-63.
- 5 SCOTT, R. W., FEIL, H. S., and KATZ, L. N. Electrocardiogram in pericardial effusion, *Am Heart Jr*, 1929, v, 68-76.
- 6 KATZ, L. N., and WALLACE, A. W. Role of cardiac ischemia in producing R-T deviations in electrocardiogram, *Am Jr Med Sci*, 1931, clxxxi, 836-843.
- 7 HOLLAND, C. W., and LEVINE, S. A. Limitations of electrocardiogram as aid in diagnosis of coronary occlusion. *New England Trans Med* 1932, ccvi, 545-551.
- 8 PROGER, S. H., and AYMAN, D. Harmful effects of nitroglycerine, with special reference to coronary thrombosis, *Am Jr Med Sci*, 1932, clxxxiv, 480-491.
- 9 LEVINE, S. A. Treatment of acute coronary thrombosis, *Jr Am Med Assoc*, 1932, xciv, 1737-1740.

CASE REPORTS

PULMONARY TORULOSIS REPORT OF A CASE *

By ROBERT M. HARDAWAY,† M.D., and PAUL M. CRAWFORD,‡ M.D., F.A.C.P.,
Sault Ste. Marie, Michigan

SYSTEMIC infections due to *Torula histolytica* are uncommon, a total of 45 authentic cases having been collected from the literature up to 1934, by Johns and Attaway¹. These authors added one case of their own. Thirty-one cases occurred in the United States. The fact that 36 cases have been reported in the past decade is a probable indication that fewer cases are going unrecognized than formerly. Previous to publication of the monograph of Stoddard and Cutler² classification of the pathogenic yeasts was based on incomplete data and the medical nomenclature of infections produced by them was in a state of confusion. At present there are available many criteria^{2, 3, 4, 5} for the identification of torula, and differentiation of torulosis from oidiomycosis. Sheppe⁴ defines torula as a yeast which multiplies by budding, does not produce ascospores, does not ferment carbohydrates and does not produce a mycelium in tissue or on culture. Oidium he defines as a yeast which multiplies by budding, does not produce ascospores, does ferment carbohydrates and does produce a mycelium when growing on culture. Rappaport and Kaplan⁵ were the first to report immunologic reactions, as determined by agglutination, absorption and complement fixation tests, in experimental animals (rabbits and guinea pigs), which had been immunized against *Torula histolytica* and against two strains of oidium. While widespread systemic infection with torula may occur, it is generally considered^{1, 2, 3, 4, 6} that this organism shows a special tendency to invade the meninges. Of 18 cases tabulated by Stone and Sturdivant³ in 1929, the central nervous system was chiefly involved in 15. The portal of entry is considered to be the respiratory tract^{3, 4, 5, 6}. Torula is widely distributed in nature, having been cultivated from wasp-nests, many grasses, plants and trees, fruits, bees, insects, canned butter, milk, pickle-brine, and soil. While several instances of pulmonary involvement have been reported as part of a systemic infection or accompanying a torula meningitis^{2, 3, 6} cases in which the lesions are limited chiefly or entirely to the lungs are exceedingly rare. Sheppe⁴ reported a case confirmed by necropsy, in which the right lung showed an organizing bronchopneumonia. There was no evidence of involvement of the central nervous system. Torula was obtained from the pulmonary lesions, grown in pure culture, and reproduced the disease by animal inoculation. Berghausen,⁷ in 1927 reported a case in which torula was isolated from an ulcer on the tongue, and in which both lungs showed infiltration not typical of tuberculosis. This case also terminated fatally, necropsy was refused. McGehee and Michelson⁸ report a case of inguinal abscess in a negro, due to torula infection, with recovery.

* Received for publication April 8, 1935.

From the Medical Service, Fitzsimons General Hospital, Denver, Colorado. Published by permission of the Surgeon General, U. S. Army.

† Lieutenant Colonel, Medical Corps, U. S. Army.

‡ Major, Medical Corps, U. S. Army.

Freeman,⁶ reviewing the literature in 1931, collected 42 cases and added one of his own. He observed that evidences of involvement in other parts of the body (than the central nervous system) are rare, that occasionally a lesion may be found in one lung, and more rarely a general infection, indicated by obtaining the torula in pure culture from the blood and urine. According to this author, lesions in the lungs may be either acute or chronic.

The pathology in the lungs^{1, 4, 5, 7, 9} is described as either a consolidation, or scattered nodules, there may be abscess formation. In the case reported by Stone and Sturdivant³ the consolidated portion of the lung had a circumscribed and well-defined outline, was firm in consistency and of grayish-white granular appearance, resembling a tumor. In another case⁴ the consolidated lung was dark brown in color, the consolidation was not as definite as that noted in lobar pneumonia at the stage of gray hepatization. Little or no tendency to pleural involvement has been reported.

Hirsch and Coleman⁹ report a case of acute miliary torulosis of the lungs, associated with torula meningitis. In a fourth case, reported by Berghausen,⁷ not confirmed by necropsy, but in which torula was isolated from an associated ulceration on the tongue, stereoscopic films of the chest showed diffuse bilateral infiltration of the lungs, the apices were apparently clear.

The case reported by Sheppe⁴ is unique in that the lesions were localized in the lung, with no evidence of invasion of other organs or systems by the fungus. This author states that the clinical findings were those of a moderate toxemia, with slight fever and leukocytosis, and that in diagnosis pulmonary syphilis, lung abscess or tuberculosis may be suspected. In the case observed by Rappaport and Kaplan⁵ nodules due to torulosis were found in the lower lobe of the right lung, with fibrocaseous tuberculous involvement of the upper lobe.

The prognosis, in cases with involvement of the central nervous system, is hopeless. All such cases collected from the literature by Stone and Sturdivant³ terminated fatally. Sheppe⁴ believes that pulmonary cases tend to recovery. No form of treatment has been proved to have any value. Iodides have been extensively used, also tartar emetic. Other drugs unsuccessfully employed include hexamethylenamine and gold sodium thiosulphate, intravenously.³ A torula vaccine has been injected intravenously.¹⁰

The following case is reported as one of localized pulmonary torulosis presenting roentgenographic evidence of lesions quite distinct from those of a pre-existing pulmonary tuberculosis.

CASE REPORT

History On February 14, 1933, P. R. G., white male, aged 33, was admitted to Fitzsimons General Hospital. The family history was irrelevant. Three years before admission he had had a roentgen-ray film of the chest made because of a severe upper respiratory infection (figure 1). This showed some infiltration, chiefly of the upper lobe. He remained at his duties until January 1933, although for the preceding three months he had had cough and expectoration.

Examination The patient was ambulant, afebrile, and not apparently seriously ill. General nutrition was good. The chest showed diminished resonance over the left upper with parenchymal râles, râles were heard also over the right mid-chest, anteriorly, and at angle of the right scapula posteriorly. The blood pressure was 100 mm. Hg systolic and 75 diastolic.

Laboratory Findings A roentgenogram of the chest showed nodose involvement, most marked in the left upper, the right mid-lung and the right base. The lesions in the right lung had a radial distribution not typical of tuberculosis (figure 2). Sputum examinations, including animal inoculation were negative for acid fast

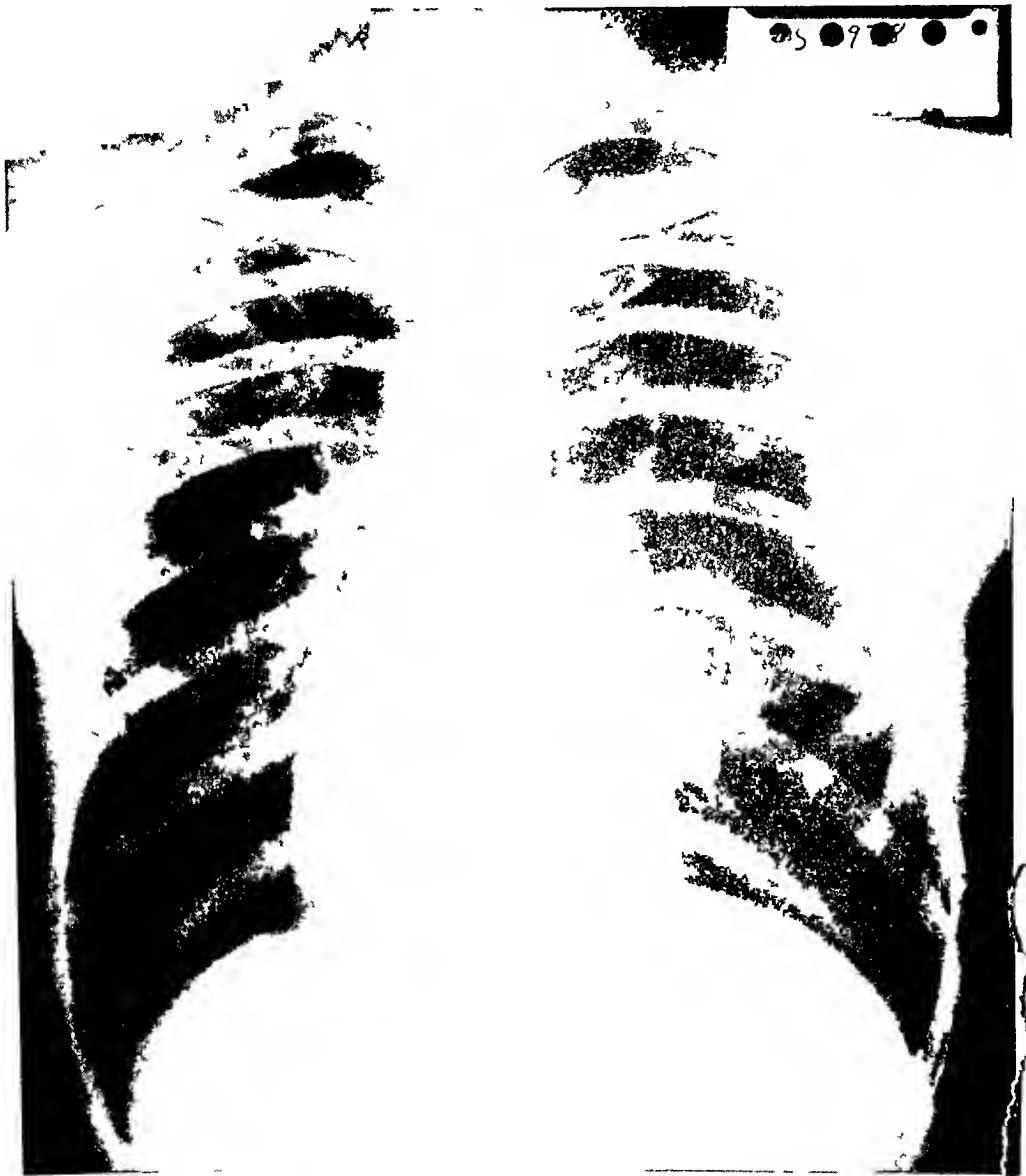


FIG 1 Roentgenogram of chest, May 20, 1930

bacilli. Yeast buds were found in direct smears and in cultures of the sputum, and were also found in smear and culture of material from bronchoscopic aspiration. Bronchoscopy showed moderate congestion of the bronchial mucosa, no free secretion was noted. This yeast was identified as *Torula histolytica*. It showed on culture a spherical budding yeast of medium size. It did not form spores on plaster blocks,

carrot agar or Gorodkova's agar. No sugars were fermented. It was highly virulent for white mice, killing in two or three days with a generalized peritonitis. The blood Wassermann and Kahn tests were negative. Spinal puncture fluid clear,



FIG 2 Roentgenogram of chest, February 18, 1933

pressure normal, cell count 6, sugar normal, globulin no increase, smear and culture showed no fungi.

Course of the Disease This was uneventful. The patient remained under observation for 15 months. During this time the pulmonary lesions showed very little change (figures 3 and 4). He remained afebrile, his weight was stationary and he

had practically no subjective symptoms. He was discharged April 30, 1934 feeling well, with slight cough and expectoration. On physical examination at discharge, râles over both sides of the chest were still heard unchanged. The patient was still feeling well when last heard from in November 1934.



FIG 3 Roentgenogram of chest, February 12, 1934

Treatment Methenamine tetraiodide (siomine) 0.65 gm, was given twice daily for two months, but discontinued because it had given rise to some digestive disturbance and had produced no appreciable effect on the roentgenographic appearance of the pulmonary lesions.

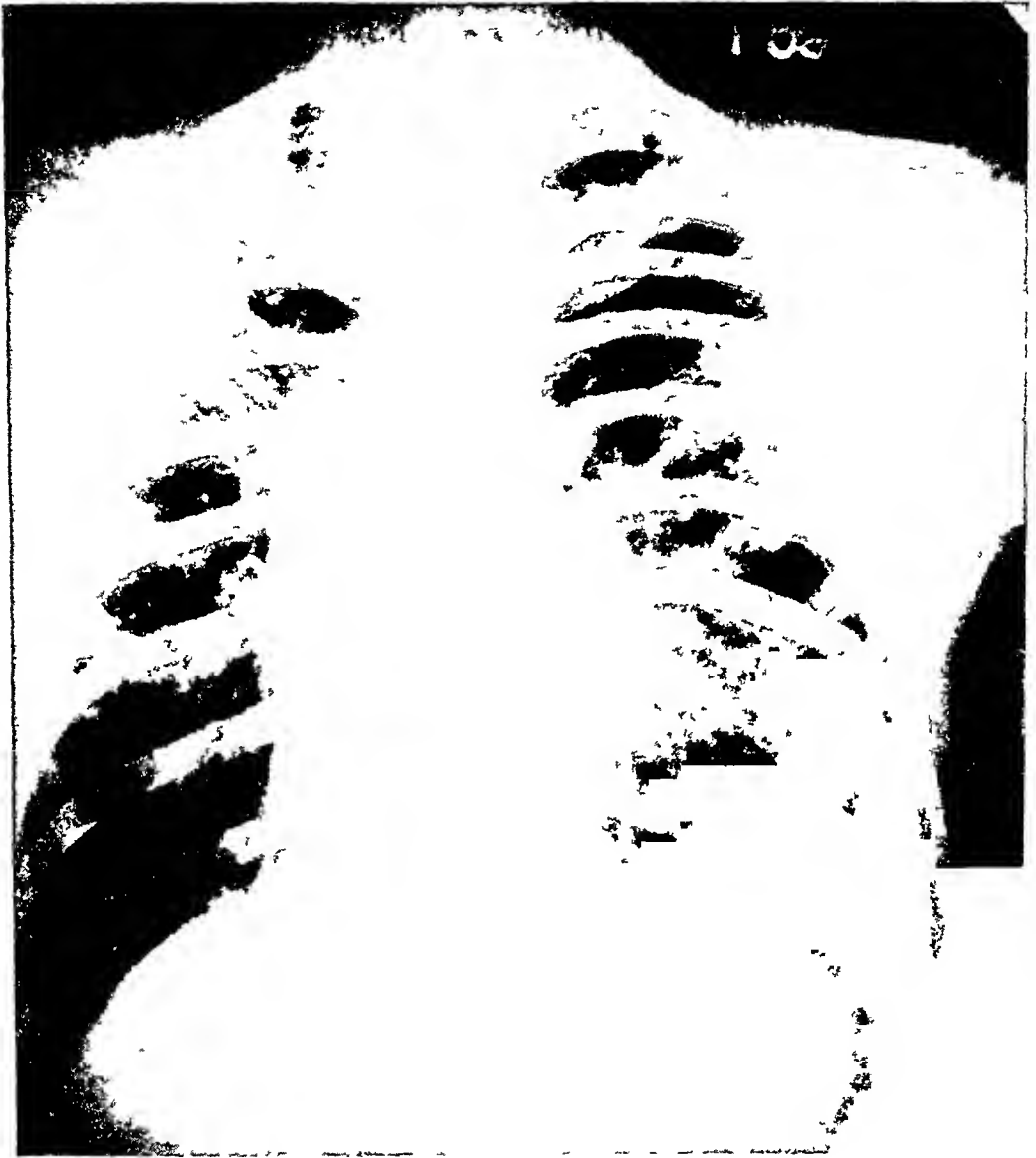


FIG 4 Roentgenogram of chest, June 22, 1934

DISCUSSION

The lesions shown in roentgenograms of the chest made in May 1930 were considered typical of pulmonary tuberculosis, however, all sputa in this case, examined at two other hospitals prior to admission to our institution, and over a period of one year while under our observation, were negative for acid fast bacilli. Animal inoculation was negative in April 1933. It is believed that this case tends to confirm the opinion expressed by Stoddard and Cutler² and Sheppe,⁴ that torulosis of the lungs offers a better prognosis than other types of infection with this organism.

Acknowledgment is made to Major Rufus L. Holt, M. C., U. S. Army, and to Dr. Arthur T. Henrici, Professor of Bacteriology, University of Minnesota Medical School, for the laboratory studies necessary in isolating and identifying the organism. Final identification, on the basis of cultural characteristics and virulence tests, was made by Dr. Henrici.

BIBLIOGRAPHY

- 1 JOHNS, F. M., and ATTAWAY, C. L. Torula meningitis, *Am J Clin Path*, 1933, iii, 459-465
- 2 STODDARD, J. L., and CUTLER, E. C. Mongi Rockefeller Inst Med Res, 1916, No. 6
- 3 STONE, W. J. and STURDIVANT, B. F. Meningoencephalitis due to *Torula histolytica*, *Arch Int Med*, 1929, xlv, 560-575
- 4 SHEPPE, W. M. Torula infection in man *Am Jr Med Sci*, 1924, clxvii, 91-108
- 5 RAPPAPORT, B. Z., and KAPLAN, B. Generalized torula mycosis, *Arch Path and Lab Med*, 1926, i, 720-741
- 6 FREEMAN, W. Torula infection of central nervous system, *Jr f Psychol u Neurol*, 1931, xliii, 236-345
- 7 BERGHAUSEN, O. Torula infection in man *ANN INT MED*, 1927, i, 235-240
- 8 MCGEEHEE, J. L., and MICHILSON, I. D. Torula infection in man, *Surg, Gynec and Obst*, 1926, xliii, 803-808
- 9 HIRSCH, E. F., and COLFMAN, G. H. Acute miliary torulosis of lungs, *Jr Am Med Assoc*, 1929, xcii, 437-438
- 10 SHAPIRO, L. L., and NEAL, J. B. Torula meningitis *Arch Neurol and Psychiat*, 1925, xiii, 174-190

PRIMARY TUMORS OF THE HEART

With Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis before Death

By SAMUEL A. SHELBURNE, *Dallas, Texas*

RARE is the opportunity to see a case of primary tumor of the heart, so the relatively little written on this subject is not surprising. Because of this rarity, the diagnosis is seldom considered before death. Gottel¹ (1919) has given Pavlowsky credit for making the clinical diagnosis of a primary tumor of the heart. The only other instances of heart tumor that have been suspected before autopsy were in patients with known primary tumors elsewhere in the body, who developed unexpected signs of heart disease, such as heart block, or cardiac decompensation (Fishberg,³ Willius and Amberg,⁵ Rosler⁴). Yater² has written a splendid review of this subject, to which the reader is referred.

I wish to present here a syndrome which was encountered in a young negro and led to a logical diagnosis of a tumor of the heart when there was no clinical sign of a primary tumor elsewhere in the body. He developed a rapid accumulation of fluid in the pericardial sac, which, on aspiration, proved to be sero-sanguinous. This was accompanied by the development of the signs of acute cardiac decompensation. The fluid reaccumulated very rapidly despite the removal of large quantities at frequent intervals. There was no fever, no history of fever, cough, night sweats, and no weight loss to suggest tuberculosis, furthermore, roentgenograms of the chest eliminated the possibility of pulmonary tuberculosis and a spinal puncture showed no evidence of tuberculous meningitis. Rheumatic pericarditis was made very unlikely both by the

* Received for publication June 14, 1934

sanguinous nature of the fluid and the absence of fever. Pneumococcus, streptococcus, or other bacterial infections, could be eliminated as possible causes for the same reasons, and the culture of the fluid was negative. Lues (gumma) would be a remote possibility and it was made even more remote by the negative results of the blood Wassermann and Kahn tests. Furthermore, the spinal fluid Wassermann and colloidal gold tests were negative. The fluid did not clot on withdrawal and the red cell count was not high enough to suggest the rupture of a blood vessel or an aneurysm leaking into the pericardium. After the diagnosis had been recorded, an electrocardiogram showed partial bundle branch block, which has been recognized as a common finding in cardiac tumor (Willius and Amberg,⁵ Rosler⁴). Therefore, we felt fairly confident of the correctness of the diagnosis and presented this case to the fourth year class as a tumor of the heart.*

We believe that, if this possibility be borne in mind when a bloody pericardial effusion is encountered, it will not be illogical to hazard this diagnosis. Two other cases of primary tumor of the heart were found in a review of 1200 autopsies and both of them had almost the same symptoms. These two cases, with complete postmortem examinations, are included in this report. It is worth while to bear in mind that, if this diagnosis can be made early, it may be possible to influence the patient's course with irradiation, as many of these tumors are of a type usually considered radio-sensitive.

CLINICAL RECORD

Case 1 S. R. was a married negro laborer, 24 years of age, who walked into the Parkland Hospital on December 12, 1933, complaining of generalized abdominal pain and distention, a hacking cough and fainting spells for a period of only five days. He stated that he was in good health, had done strenuous labor until the onset of the above symptoms, and had noticed no fever, sweats, or chills, and no hemoptysis. Since the onset he had developed persistent generalized colicky pains in the abdomen and an increasing feeling of distention, which was only partially relieved by bowel movements. This pain was not relieved by soda and had no relation to meals, or to the type of food. He had fainted, without warning, two or three times during this period. He thought he had been a little short of breath but was not sure. There had been no swelling of the legs.

He had had an easily cured penile lesion eight years previously. The past history was otherwise negative. The family history was irrelevant to his present condition.

On his admission examination, he was described as a well nourished and developed young negro, not acutely ill. The systolic blood pressure was 120, the diastolic 90, pulse 80, respirations 20. The temperature was 97.3° F and varied from 97° to 98° until a few hours before death. The skin was normal. There were no enlarged lymph nodes. The pupils reacted to light and accommodation. The heart was moderately enlarged, the sounds distant, but there were no murmurs. The lungs were normal, no râles were heard at apices or bases. The liver was enlarged and tender, and there was moderate abdominal distention. The rectal examination and the genitalia were negative.

*It is interesting to contrast the method of diagnosis in this case with the keen reasoning and erudition shown by Pavlovsky in his case of a primary tumor of the heart. He noticed that his patient had the signs and symptoms of mitral stenosis when sitting or standing, but not when lying down. This suggested a tumor in the left auricle, which fell into the mitral orifice when the heart was vertical. The tumor was present but was in the right auricle.

The blood Wassermann and Kahn tests were negative. A spinal puncture was done and the pressure was 30 mm Hg, but the fluid was normal to all tests, including Wassermann and colloidal gold. The hemoglobin was 80 per cent, red blood cells 3,970,000, white blood cells 8000, with normal differential count. The urine specific gravity was 1032, it contained no sugar but did contain one plus albumin. A moderate number of hyaline casts and about 50 pus cells per low power field were found. The blood sugar measured 105 mg, urea nitrogen 32 mg, and creatinine 1.5 mg per 100 c.c. Two sputum examinations revealed no tubercle bacilli, and few pus cells.

The diagnosis at this time was uncertain. On December 16, the patient began to cough up blood-stained sputum, but there was no fever. He was very uncomfortable with some dyspnea and had to have morphine for relief. The next morning he was found with the signs of fully developed cardiac decompensation, with extensive pitting edema and dyspnea, but he never became orthopneic. There was great enlargement of the area of cardiac dullness and the heart sounds were distant. The diagnosis of pericardial effusion was suggested and a roentgenogram of the chest confirmed this. The acute decompensation was thought to be due to the rapid accumulation of fluid in the pericardial sac.

In the early evening, I was asked to see the patient and the following notes were made on the clinical record: "This morning, he awoke with extensive edema. There is marked increase in the venous pressure. There is an enormous increase in the precordial dullness and it rises high on the left upper border. There is no Broadbent sign. The condition is suggestive of pericardial effusion, as first postulated by Dr. Swift." Dr. Swift then withdrew about 900 c.c. of bloody fluid which did not clot. The dullness decreased on the upper border but not on the left border. The patient experienced little relief.

The next morning the writer made the following note: "The eye grounds are negative. The patient is still very ill. Precordial dullness is still very wide, the sounds distant. Dullness is now present at the left base with egophony and rales (either pneumonia or compression of lung from pericardial effusion). The best possibilities here seem to be (1) tumor of the heart and pericardium, primary or secondary, (2) tuberculosis of the pericardium, (3) acute pericarditis, associated with pneumococcus septicaemia, or a local infection (as rheumatic), (4) gumma of the pericardium. When other signs are considered (no fever, etc.), I believe this is a pericardial and cardiac tumor, either primary or secondary." There was no evidence made out clinically of a primary tumor elsewhere.

An electrocardiogram (December 18) showed a rate of 95, regular rhythm, P-waves normal, P-R interval 0.16 second, QRS slurred and slightly notched in all leads, main deflections downward in Lead I and upward in Leads II and III. QRS intervals, 0.16 in Lead I, 0.12 in Lead II, 0.16 in Lead III. The T-waves were diphasic in Lead I and Lead II and flat in Lead III. The picture was typical of that of partial bundle branch block. Complete block and bundle branch block have been used in the past as evidence of tumor of the heart in cases with known malignant growths elsewhere (Rosler, Willis and Amberg).

We were unable to relieve the patient's distress by repeated pericardial aspiration. The fluid always presented the same bloody appearance. Laboratory study showed it to contain 1,250,000 red blood cells, 1,400 white blood cells, lymphocytes 91 per cent, polymorphonuclear leukocytes, 9 per cent. Culture yielded no growth.

These subsequent developments confirmed our belief that the most logical diagnosis was tumor of the heart. At a clinic for fourth year students we based this on the following considerations: (1) the rapid reaccumulation of a bloody fluid suggested tumor, (2) tuberculosis was unlikely, as there was no clinical or roentgenographic evidence of pulmonary phthisis, (3) acute infections as pneumonia, streptococcal septicemia, or rheumatic fever, were ruled out by the nature of the cells in

the fluid lack of fever and leukocytosis, (4) lues was unlikely because of the negative blood and spinal fluid Wassermann tests, (5) rupture of a vessel into the pericardium was ruled out by the comparatively low red cell count and the fact that the fluid did not clot.

The patient was desperately ill at this time, and it was hoped that drainage, more adequate than aspiration, would relieve him so that subsequently irradiation therapy could be tried. A pericardiotomy was therefore performed by Prof. Weaver on December 19 and exposed a massive invading tumor confined to the left auricle and upper half of the left ventricle. Drains were left in place and the wound closed.

The patient died about eight hours after the operation, and permission was granted for only a partial autopsy. The tumor seemed to be confined to the heart. It involved a large part of the left auricle, invaded the auriculo-ventricular septum, and extended into the left ventricle about half way to the apex. It was not in any sense circumscribed but seemed to be growing in every direction. The tumor was a pale, reddish gray color. A large mass 5 by 5 cm. was removed for microscopic study but we were unable to obtain the entire heart. The liver could not be palpated soon after death. Doubtless the enlargement before operation was due to passive congestion.

Microscopic Examination The specimen submitted for microscopic study consisted of one main mass measuring 3.5 by 1.5 by 1.2 cm., a second mass about two-thirds as large, and several other smaller fragments. Sections prepared from the two main masses of tumor tissue presented strikingly different structures.

One representative area of tumor (figures 1 and 2) is formed of loosely spaced cells with rounded nuclei and varying amounts of cytoplasm. The nuclei possess moderate amounts of chromatin and appear slightly vesicular. A single prominent nucleolus is present in many of the nuclei. The outer border of the cytoplasm of the tumor cells is often irregular and sometimes indefinite, and delicate processes seem to arise from many of the cells. No definite grouping of the tumor cells is evident except in regions where degenerative changes are marked. In these regions, the tumor cells are closely packed about the unobstructed blood vessels of the area, with slightly longer axes vertical to the walls of the vessels. Mitotic figures are only moderately numerous and the variations in chromatin content of the nuclei of the tumor cells are not marked. The nuclei are of fairly uniform size, and only an occasional larger and more hyperchromatic nucleus is seen. This area of tumor is imperfectly and coarsely lobulated by bands of mature fibrous tissue composed of coarse collagen fibers. In some regions these fibrous bands are edematous and a few recent hemorrhages are seen in focal areas, while other areas contain a brownish blood pigment having the appearance of hemosiderin. More delicate fibrous strands with moderately large and well developed blood vessels extend into the masses of tumor cells constituting the lobules of the tumor. In some regions much of the tumor is necrotic and the blood vessels of these areas frequently contain fibrin thrombi.

Sections from a different portion of the tumor (figures 3 and 4) reveal a spindle cell structure in striking contrast to the portion of the tumor above described. The tumor in this portion is more compact, and appears distinctly fibrous. The tumor cells are arranged in bands which have a tendency to form indefinite whorls. The nuclei are mostly oval or spindle shaped, their moderate chromatin content is distributed in granular form. Nucleoli are present, but are slightly less conspicuous. The cytoplasmic masses are elongated and apparently possess processes. In some areas, the cytoplasm appears vacuolated, the nucleus being surrounded by scattered protein granules. Where vacuolization is most marked, the tumor tissue has a reticulated appearance, and the fibrous structure is less prominent. A few recent hemorrhages and hemosiderin pigment are present in widely scattered focal areas. The intercellular substance is formed of delicate fibrils together with a granular

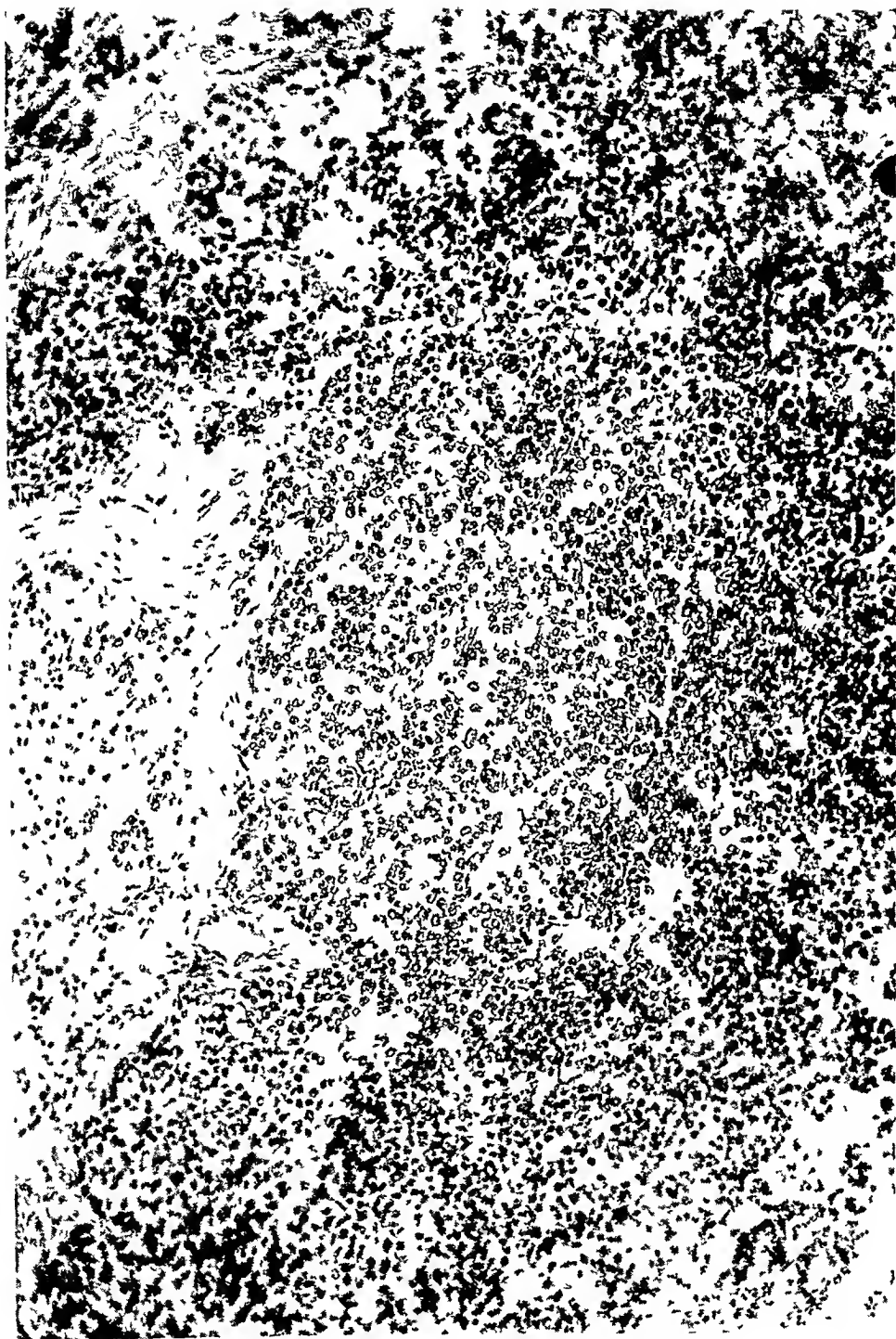


FIG 1 Heart tumor Low power magnification shows undifferentiated cells of irregular rounded type

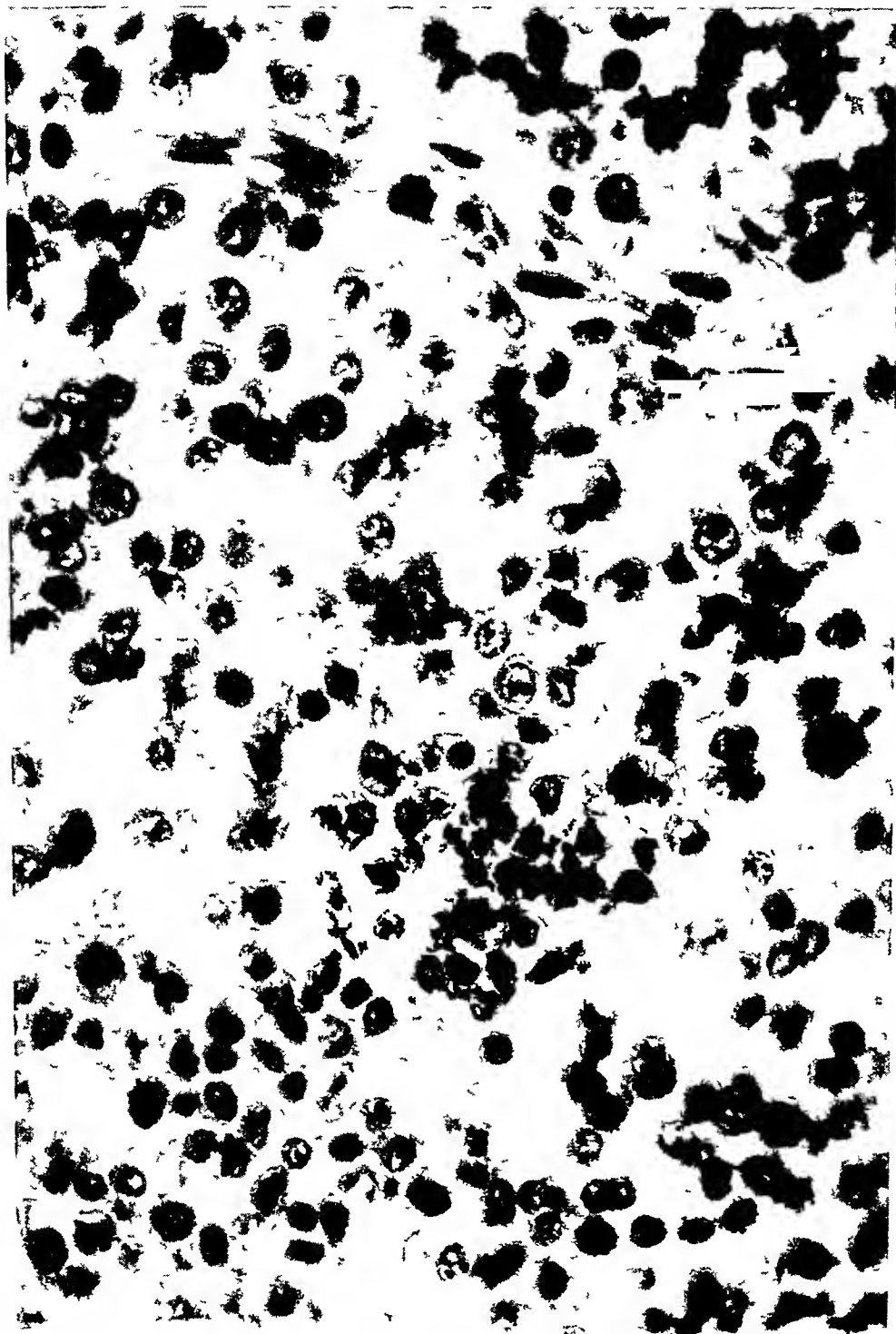


FIG 2 Heart tumor Higher magnification shows cell detail of undifferentiated round cell area

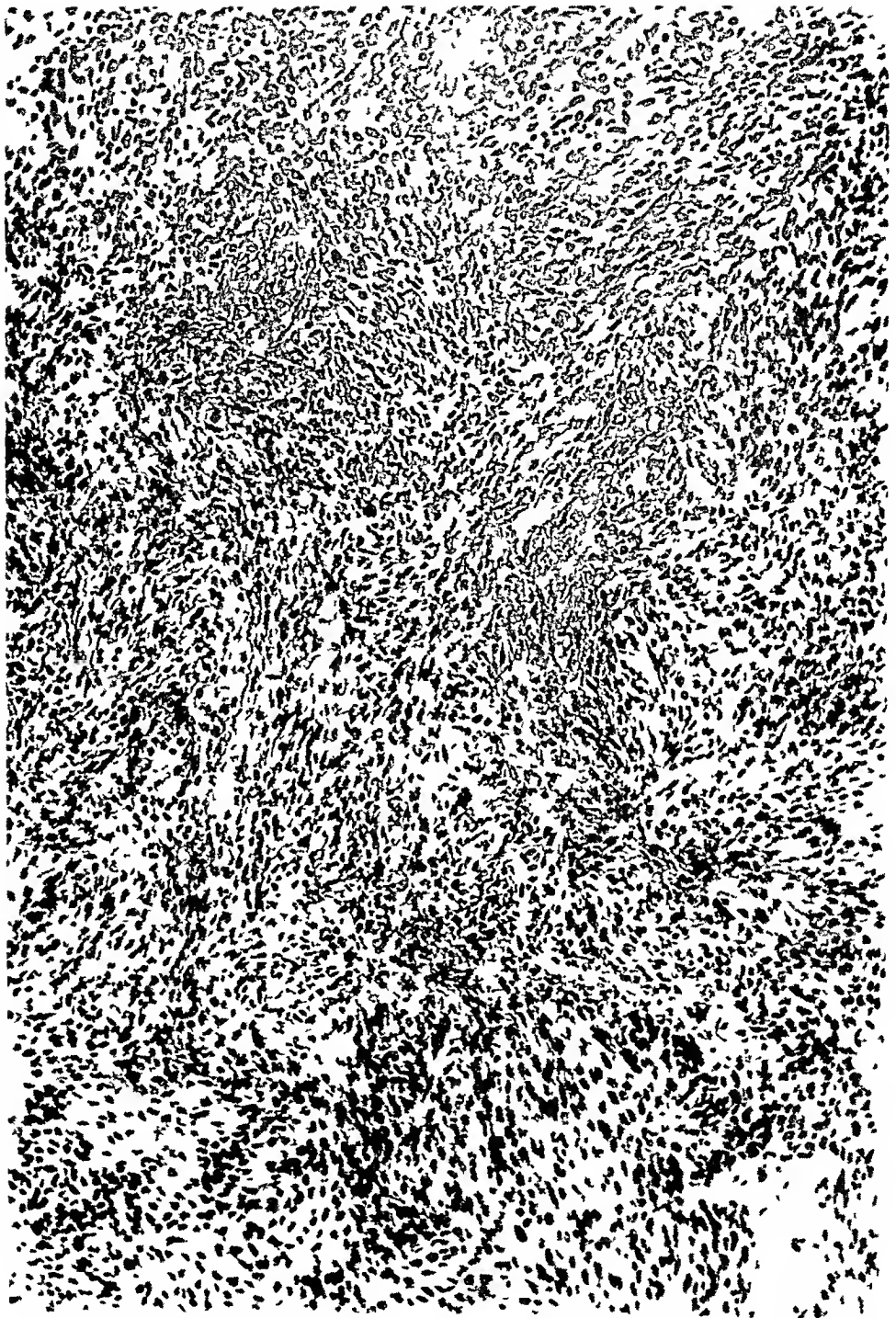


FIG 3 Heart tumor Low power magnification shows more differentiated area composed of spindle-shaped cells



FIG 4 Higher magnification shows cell detail of more differentiated area composed of spindle-shaped cells

precipitate similar to that of edematous tissues. Mitoses are infrequent and nuclear variations are not marked.

The appearance is that of a moderately well-differentiated, invasive tumor of sarcoma type. Although the histogenesis of this tumor has not been determined, its structure suggests a peripheral nerve origin.

Prof. George T. Caldwell found two other cases of primary tumor of the heart in the records of the Department of Pathology of the Baylor University with careful and complete autopsy reports on each. He has added our case (case 1) to these as a part of his exhaustive study of the pathological findings which he will report later. It is important to note that the microscopic features on the tumor in case 1 are almost identical with those of case 2. The origin of the tumor in the latter was proved by a complete autopsy to be in the heart.

The clinical features of the earlier cases were very similar to those of case 1, but in neither of these was the pericardial effusion suspected. Both patients were young individuals with an acute onset of decompensation, with no previous history of heart disease or any discoverable cause for heart disease. There was no fever and no evidence of tuberculosis and both had negative Wassermann tests.

Case 2 B. J. H., a white woman 22 years old, was admitted to the Baylor Hospital on September 6, 1932, complaining of a persistent hacking cough and epigastric pain for eight days. She had had nausea and vomiting during an otherwise normal pregnancy, which had terminated seven weeks before. The nausea and vomiting increased with the onset of the above symptoms.

On examination she was described as a young, fairly well developed white woman lying in bed and vomiting small amounts of yellow fluid. The temperature varied from 97° to 98° F during the four days in the hospital and the pulse fluctuated from 100 to 116, the respirations from 18 to 22. There was edema of the eyelids, face and legs, also evidence of free fluid in the abdomen. The edema increased rapidly during the next three days. There was slight cyanosis. The apex beat of the heart was thought to be within the mid-clavicular line. The heart sounds were of good quality, blood pressure, systolic 110, diastolic 80. The liver was felt 12 cm. below the costal margin. The symptoms increased, but no new physical findings were made out. She died on the fourth day after admission.

Laboratory studies. The Wassermann test was negative, the hemoglobin 65 per cent, red blood cells 3,560,000, white blood cells 12,000 to 18,000, with 80 per cent polymorphonuclear leukocytes. The urine showed a small amount of albumin, many hyaline and granular casts, and a few red blood cells. The blood urea was 85 mg. and blood sugar 115 mg. per 100 cc.

The autopsy revealed about 1000 cc. of bloody fluid in the pericardial sac. There was a large, firm, yellowish tumor mass in the left ventricle, posteriorly and anteriorly along the septum and several smaller masses about the base of the heart attached to the great vessels. There were secondary tumors in the lungs and pleura, and a metastatic mass in the right suprarenal gland. The liver was not found enlarged. Doubtless the antemortem enlargement was due to extreme congestion. Microscopic examination of the tumor showed a primary sarcoma of the heart, very similar in appearance to the tumor in case 1.

Case 3 F. C., a 38 year old Mexican, was admitted to the Parkland Hospital in January 1926, complaining of cough of two weeks' duration, dyspnea, swelling of the abdomen and legs for the past three weeks. He also stated that he had had pain in the left shoulder, back and left side of the chest of increasing severity for three years.

Dyspnea and general anasarca were noted on examination. The pulse rate was 60 and irregular, respirations 20. There was no fever. The heart sounds were weak and distant, and the precordial dullness extended past the mid-axillary line into the sixth interspace. The apex beat was neither seen nor felt, and no murmurs were heard. The lungs were clear on percussion and auscultation. The abdomen was distended with fluid, and the liver and spleen were not palpable.

Laboratory examinations. The Wassermann test was negative, the hemoglobin was 80 per cent, the red blood cells numbered 4,840,000, white blood cells 9,650, polymorphonuclear leukocytes 70 per cent. The blood urea and sugar were normal. The sputum contained no acid-fast bacilli. A chest roentgenogram showed an enlargement of the heart shadow. The lung fields were clear.

At autopsy a large pericardial sac contained 1500 cc of bloody fluid which was not clotted. The heart was not enlarged, but the surface, especially over the left auricle and ventricle, was roughened by thick nodular areas which were seen and felt beneath the epicardium. The endocardium and valves were normal. There were no metastatic lesions except in a peribronchial lymph node, and this was only about 0.2 cm in diameter. Ascites, a serous effusion in the right pleural cavity, generalized edema and passive congestion of the viscera were noted. The liver was not enlarged.

The microscopic sections proved the tumor to be a mesothelioma of the pericardium.

SUMMARY

This report, the second in medical literature, describes the signs, symptoms and histologic appearance of a primary tumor of the heart which was correctly diagnosed before death. According to Gottel (1919), the first clinical diagnosis of this condition was made by Pawlowsky. The differential diagnosis which led to the correct assumption in this instance was also found applicable in two others found among autopsy records, it should lead more frequently to the correct diagnosis, whenever an otherwise unexplainable bloody pericardial effusion is encountered. Other signs and symptoms have not infrequently led to a diagnosis of secondary tumor, but are unreliable in the diagnosis of primary tumors.

I wish to thank Prof. George T. Caldwell for his aid and encouragement.

BIBLIOGRAPHY

- 1 GOTTEL, L. Ein Fall von primären Herztumor, *Deutsch. med. Wchnschr.*, 1919, *xli*, 937.
- 2 WATER, W. M. Tumors of heart and pericardium, *Arch. Int. Med.*, 1931, *xlvi*, 627-666.
- 3 FISHBERG, A. M. Auricular fibrillation and flutter in metastatic growths of right auricle, *Am. Jr. Med. Sci.*, 1930, *clxxx*, 629-634.
- 4 ROSLER, O. A. Vier Seltene Herzbefunde ein Beitrag zur Herz Diagnostik, *Zentralbl. f. Herz u. Gefasskr.*, 1924, *xvi*, 261.
- 5 WILLIUS, F. A. and AMBERG, S. Two cases of secondary tumors of the heart in children, in one of which diagnosis was made during life, *Med. Clin. N. Am.*, 1930 *xiii*, 1307-1316.

EDITORIAL

THROMBOPEMIC PURPURA

To Kaznelson's original suggestion of nineteen years ago, that splenectomy is a curative measure in thrombopenic purpura, little more has been added. The disorder, as earlier, retains its main divisions, as occurring in a primary or idiopathic form, and in a symptomatic variety secondary to other disorders. Although we are essentially concerned with the primary form, the existence of the secondary form is of the utmost diagnostic importance for the reason that in this secondary form splenectomy is not only contraindicated but may be actually harmful. The conditions most frequently giving rise to symptomatic purpura are sepsis, infectious diseases, drug poisoning, atypical acute leukemia, and aplastic anemia, the last being the most important.

At the time of Allen Whipple's review of cases in 1926, about 100 operations had been performed and the early results had amply confirmed Kaznelson's contention. Whipple's cases were divided into two groups representative of both the acute and the chronic variety, the former including so-called purpura fulminans, a rapidly fatal form uncontrolled by any known means. The operative mortality was about as one would expect with this type of risk, 8 per cent in the chronic cases and 90 per cent in the acute. This was the first crystallization of opinion based on a large collected series of cases and, while most useful, could necessarily give only limited information regarding the late stabilized effects of splenectomy on the natural history of the disease. We have as yet no knowledge based on well considered accumulated experience that answers the question, when, exactly, should splenectomy be performed. When should the clinician, on whose shoulders rests the responsibility, definitely recommend that the spleen be removed?

As inferred, the indications for operation are not so clearly outlined as to make the clinician's task an easy one. It will be agreed that as an emergency measure for acute purpura, when excessive bleeding cannot be controlled by any other means now known—rest, transfusion or irradiation—splenectomy should be performed, provided always that the form of purpura present is definitely primary. Palliative measures being of no avail, it remains for the surgeon to perform as safeguarded an operation as possible, accepting a high mortality in the hope of saving an occasional patient among a group otherwise doomed.

Chronic purpura, or purpura of less severity, offers opportunity for greater differences of opinion. A common problem of this type is the case seen during a prolonged mild attack or in one of a series of recurrences. The degree of platelet reduction may be only moderately severe and quite usually all of the other signs and symptoms are relatively mild. Yet since the diagnosis is primary thrombopenic purpura such a case faces potential

dangers The clinician confronted by such a situation today will search vainly for sufficient data to enable him to answer confidently the questions which inevitably arise Will the patient outgrow this disorder? Does spontaneous cure ever occur? Is the tendency of this particular patient toward recovery, toward greater severity, or if toward immediate recovery, toward increasingly severe attacks? If the patient under observation gives some indication of immediate recovery, should splenectomy be recommended at once, should it be deferred until recovery is apparently complete and then performed—an "interval splenectomy", or should it be deferred until another more acute and less controllable attack occurs? These questions are answered differently by different men, and the lack of agreement no doubt must be due to insufficient or contradictory experiences

How useful it might prove if there existed a "Purpura Registry" comparable to the Bone Tumor Registry of the American College of Surgeons The function of such a registry could be the collection and study of the early and late histories of all cases of purpura Most useful, too, would be the study of cases in which splenectomy had not been performed Such a collection might reveal much now unknown concerning the natural history of the disease Many would like to know more of the connection between the appearance, or the exacerbation of symptoms in apparently true idiopathic purpura, and upper respiratory infections or tonsillitis What effect does tonsillectomy have in these cases? Have any of these patients, in whom splenectomy for one reason or another has been avoided, subsequently died in an acute attack?

Study of the therapeutic management of these cases in groups sufficiently large for comparison would decide between well known differences of opinion For example, regarding transfusion, there is no unanimity as to whether or not the direct method offers advantages over the indirect The amounts, frequency, and timing of transfusions with regard to operation are other uncertain features

In the group operated upon, what percentage has subsequent bleeding? How severe or fatal are these recurrences? A registry of these cases might result in more complete late studies, with regular or seasonal observations It might conceivably uncover certain features common to groups of cases whose subsequent courses have been similar

A surgeon who has had the experience of operating on fairly acute cases of thrombopenic purpura, who has found it necessary literally to line his incision with hemostats, and then after removal of the spleen, even while closing the abdomen, has been amazed at the dryness of the wound, is apt to be more convinced of the specificity of the operation than is his medical colleague who may, during the succeeding months, observe one or more relapses of symptoms usually, however, much less severe than before the operation A study of such operative and postoperative results would furnish a basis for convictions regarding treatment of the so-called chronic or only moderately severe cases

The opinion of some today is that since we have insufficient basis for prediction as to the future serious dangers confronting the individual mild case of chronic thrombopenic purpura there is less risk in an immediate splenectomy than in expectant treatment. The risk of a properly conducted operation even in moderately severe cases may well be less than that of a deferred operation in the same case undertaken finally as a last resort.

Whether this or some quite different policy will eventually prove to be best founded can be determined only through further study and especially through systematic pooling of experience with treatment of the disease.

EDWARD M. HANRAHAN

REVIEWS

Clinical Management of Syphilis By ALVIN RUSSELL HARNES M D 71 pages, 14.5 × 22 cm Macmillan Co., New York 1935 Price, \$1.50

The author discusses the problem of the therapy of syphilis and furnishes practical schedules of treatment according to the stage of the disease. The importance of system and a definite plan is stressed. Complicating factors such as cardiovascular involvement are dealt with rather briefly. In discussing post-arsphenamine reaction the warning value of itching and of slight icterus should have been emphasized. Dr. Harnes is almost alone among syphilologists in recommending sulpharsphenamine. In spite of the drawbacks necessarily present in such a brief discussion of an important subject, this small book will have a definite value for the general practitioner.

H M R

Food and Health By HENRY C SHERMAN 296 pages, 14 × 20.5 cm The Macmillan Co., New York 1934 Price, \$2.50

This book is written in simple, non-technical language. Its chief purpose is "to guide the reader to well-balanced judgments in the daily choice and use of food." The solid and noteworthy contributions of the author to the science of nutrition, as well as his widely used treatises on the Chemistry of Food and Nutrition and on Food Products, which are well recognized standard works of reference, make anything he says worthy of respect and attention. It must, however, be confessed that there is little that is very new in this work or that has not been quite as well and attractively presented elsewhere. The author is emphatic in driving home the thesis that at least half of the food calories of the diet should be in the form of the "protective foods" and that at least half of whatever cereal products are consumed should be of the whole grain variety. The last third of the book is devoted to tables of the caloric values of the customary servings of foods, of their content in proteins and minerals, of vitamin values, and of illustrative records of actual meal menus—one prolonged over a period of six months. There is an interesting bibliography of publications on diet and nutrition, largely recent, and a good index. One is always impressed with the debt which every author of books on food and nutrition owes to the publications of the United States Department of Agriculture, an obligation which Dr. Sherman candidly acknowledges on page 208.

G A H

The Nervous Patient By CHARLES PHILLIPS EMERSON, M D 463 pages, 14 × 21 cm J. B. Lippincott Co., Philadelphia 1935 Price, \$4.00

This volume is an attempt to supply a clearer understanding of the emotional components of the patients who come into a general practitioner's office. The first five chapters (of thirty) present the author's views of the allergic and autonomic endocrine mechanisms by which physical symptoms are produced. The next thirteen chapters go through the body by symptoms, ostensibly to point out the nervous concomitants of various disease pictures.

This is all done in 176 pages filled with various symptoms which "may occur" or are "not infrequently seen." It reminds one of the paragraphs in many texts in which the more unusual variations of common chemical syndromes are mentioned, and is not a satisfying presentation. The psychological aspect of treatment is rarely more than referred to.

The remaining twelve chapters take up sleep disorders, disturbances in the sex life, the psychoneuroses and the psychoses. It is a superficial study. The psychopathology is a mixture of various schools of thought. We doubt if many psychiatrists would agree with any of the formulations. Treatment is by rest, diet, nightly reading of the Psalms and exhortations to make "social efforts with high spiritual aims." Bromides are prescribed in large doses. Psychoanalysis and intensive psychotherapy are dismissed with a mention. The newer concepts are not mentioned.

In spite of all this, it is not a bad book. After all, when a "nervous patient" comes into the office the physician wants to know what to do about it. In this book he will find treatment outlined in some detail. Psychiatrists would sniff at it but no doubt a great many patients may be relieved of their most troublesome symptoms by the means Dr. Emerson suggests.

H M M

Public Health Nursing in Industry By VIOLET H. HODGSON, R.N., Assistant Director of the National Organization for Public Health Nursing, foreword by C-E A. Winslow, Dr. P.H., Yale University. xii + 249 pages, 14 x 20 cm. Macmillan Company, New York. 1933. Price, \$1.75.

The purpose of this book, "to indicate the potential field of public health nursing in commerce, trade and industry," is well brought out both from the viewpoint of the nurse engaging in this type of work and of the organizations needing this service. It opens up to the nurse a vast undeveloped field needing leaders and workers for building up health programs for employees as well as the curative and rehabilitative work to which we have become accustomed. For the executives there are many points pertaining to the position of the nurse in industry, many suggested possibilities for development in the various organizations resulting in better health of employees and thereby increased output of production.

The book is divided into two parts, Part I dealing with Company Organization and Administration, Part II with Nursing Service, The Principles, Practices and Procedures. The material is well arranged for easy reference and written in a simple but stimulating style. Many ideas and suggestions are given for planning, organizing and equipping such a department, as well as for complete and accurate record-keeping.

The personality and qualifications of the industrial nurse are also included. The need for a deep interest in people and for "the ability to make her services freely accessible," however, does not seem any reason for a departure from a professional bearing. While this type of nursing is a specialty and requires postgraduate courses for filling many of the higher positions, it is possible, though in all too few schools, to receive a course in Public Health Nursing in the basic undergraduate course which will fit one for many positions in this field.

Roots of Crime: Psychoanalytic Studies By FRANZ ALEXANDER, M.D., Director, Chicago Institute for Psychoanalysis, and WILLIAM HEALY, M.D., Director, Judge Baker Guidance Center, Boston. 305 pages. Alfred A. Knopf, New York. 1935. Price, \$3.00.

This book presents the case histories of 11 criminals, 10 men and one woman, who were studied and treated by the psychoanalytic technic as applied by Dr. Alexander. Seven of the cases were reported as successful analyses, and four as unsuccessful attempts. This project was a piece of research undertaken to determine, if possible, the traits that are likely to produce delinquency and at what age they begin. The study was financed by a grant from the Julius Rosenwald Fund.

This new approach to the study of the criminal is painstaking and time-consuming, and as such it is recognized that it can be applied to only a few cases. Nevertheless, the authors in attempting to explore the causations of certain types of criminal careers, pursued a path that science, particularly in medicine, recognizes as offering the greatest promise of showing new ways to therapeutic achievement. The psychoanalytic method is extremely expensive, but if it could be applied to selected cases the expense would be nothing as compared with the social costs of long continued careers of criminality.

This study brings out the fact that some individuals, given chances for a normally pleasurable life after making a start in the paths of delinquency, find themselves unable to cease their delinquent trends under the very environmental circumstances which they themselves in full consciousness declare to be most desirable. These case histories demonstrate that any ordinarily or even extraordinarily good environmental changes may not bring about the desired checking of antisocial impulses when from early years unconscious motivations or drives have existed. Emotional factors of all kinds have been found active in creating inner tensions which the individual attempts to relieve by criminal acts.

Dr William Healy has for many years been working in the field of criminology and was the first physician systematically to use the psychiatric approach in the study of the delinquent and criminal. He has contributed many books on the subject to medical literature and his name connected with this book unreservedly recommends it for serious perusal.

J L McC

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members

- Dr E Cowles Andrus (Fellow), Baltimore, Md —1 book,
“Physical and Clinical Diagnosis”,
 - Dr Lee D Cady (Fellow), St Louis, Mo —1 reprint,
 - Dr John L Goforth (Fellow), Dallas, Tex —1 reprint,
 - Dr Noxon Toomey (Fellow), Palmyra, Mo —3 reprints,
 - Dr Frank L Williman (Fellow), Washington, D C —1 reprint,
 - Dr V W Bergstrom (Associate), Binghamton, N Y —3 reprints,
 - Dr Hyman I Goldstein (Associate), Camden, N J —1 reprint
-

Through the initiative of Dr Ignacio Chavez (Fellow), Mexico City, the “Mexican Society of Cardiac Studies” was founded and organized on May 27. The official headquarters of the Society is Artes 5, Mexico, D F. The studies of the Society will be published in “Archivos Latino Americanos de Cardiologia y Hematologia”. Dr Ignacio Chavez was elected the first President and Dr Jose Quintin Olascoaga was elected Secretary-Treasurer.

The following Fellows of the American College of Physicians will contribute to the Program of the Mississippi Valley Medical Society Meeting, known as the Tri-State (Illinois, Missouri and Iowa) Post-Graduate Assembly, at Quincy, Ill, October 2, 3 and 4

- Dr William C MacCarty, Professor of Pathology, University of Minnesota Graduate School of Medicine, Rochester, Minn ,
- Dr Albert Sorland, Chairman of the Malignancy Board, California Hospital, Los Angeles, Calif ,
- Dr E Sanborn Smith, member of the Missouri State Board of Health, Kirksville, Mo ,
- Dr D G Stine, Professor of Medicine, University of Missouri School of Medicine, Columbia, Mo ,
- Dr G M Cline, Head of the Department of Pediatrics, Brokaw Hospital, Bloomington, Ill ,
- Dr F G Norbury, Associate Physician to the Norbury Sanatorium, Jacksonville, Ill

Dr Harold Swanberg (Fellow) Quincy, Ill, is Secretary-Treasurer of the Society

Dr William Devitt (Fellow), Physician in Charge and Superintendent of Devitt's Camp, Allenwood, Pa, was recently elected President of the Federation of American Sanatoria at the Federation Meeting in Albuquerque, N M

Dr Simon R Blatteis (Fellow) was recently appointed Chief of the Department of Medicine at the Jewish Hospital at Brooklyn

Dr Frank H Krusen (Associate) has been appointed Director of the Section on Physical Therapy at the Mayo Clinic, Rochester, Minn

Dr Louis H Behrens (Fellow), St Louis, Mo, presented a paper on "Hyperpituitarism, A Report of Two Interesting Clinical Cases" on the recent Pan-American Medical Congress cruise to South America. The one case was the now well known "Alton Giant," whom Dr David Barr (Fellow) and he have reported and observed now over five years

Dr George J Wright (Fellow), Pittsburgh, has been appointed Professor of Neurology at the University of Pittsburgh School of Medicine, to succeed the late Dr Thomas M T McKennan

Dr Henry S Plummer (Fellow), Rochester, Minn, was the recipient of the honorary degree of Doctor of Science by Northwestern University at its last annual commencement

Dr Albert C Broders (Fellow), Rochester, Minn, has recently accepted the appointment of Professor of Surgical Pathology and Director of Cancer Research at the Medical College of Virginia, Richmond

Dr Hugh J Morgan (Fellow) has been appointed Professor of Medicine at Vanderbilt University School of Medicine, Nashville, succeeding Dr Charles Sidney Burwell, who has been elected Dean and Professor of Research Medicine at Harvard University Medical School

Dr Vincent J Dardinski (Associate) has been advanced to Professor of Anatomy and Director of the Department at the Georgetown University School of Medicine, Washington, D C

Dr John T Farrell, Jr (Fellow) has been made Assistant Professor of Roentgenology at the Jefferson Medical College of Philadelphia

Former associates of the late Dr Aldred S Warthin (Master), the first Editor of the ANNALS OF INTERNAL MEDICINE, recently presented to the University of Michigan School of Medicine a bronze plaque as a memorial to Dr Warthin. Dr Warthin had been for many years Professor of Pathology and Director of the Pathological Laboratory

Dr Ernest R Zemp (Fellow) Knoxville, has been made President of the Tennessee Valley Medical Association

Dr Howard T Karsner (Fellow), Professor of Pathology at Western Reserve University, has been elected to membership in the French Association for the Study of Cancer

Dr Millard E Winchester (Fellow), Brunswick, Ga, commissioner of health of Glynn County, was recently tendered a dinner by the Brunswick Board of Trade,

in recognition of his county's winning first prize in the southeastern division of a rural health contest sponsored by the U S Public Health Service and the Chamber of Commerce of the United States. This county was the first in the state of Georgia to have the services of a paid health officer

The Washington Society of Pathologists tendered a farewell banquet to Major Virgil H. Cornell, Secretary-Treasurer of the Society and retiring Curator of the U S Army. Lt. Col. William Denton (Fellow) is the new Curator and has been elected Secretary of the Society

Dr. Coursen B. Conklin (Fellow) has been reelected Secretary of the Medical Society of the District of Columbia

Admiral Cary T. Grayson (Associate), Chairman of the American Red Cross, was recently appointed Chairman of the League of Red Cross Societies

Dr. Louis H. Fligman (Fellow), Helena, Mont., was installed as President of the Medical Association of Montana, at its last annual meeting during July

Dr. Jonathan C. Meakins (Fellow), Montreal, Que., Ex-President of the American College of Physicians, has been made a Fellow of the Royal College of Physicians of London

Sir Frederick Banting (Fellow), Professor of Medical Research at the University of Toronto, was the recipient of the gold medal of the Society of Apothecaries of London, June 4, "for valuable services rendered to the science of therapeutics." Dr. Banting was also made a Fellow of the Royal Society, and on June 20 delivered an address on the history of insulin at the British Postgraduate Medical School, Hammersmith

Dr. James B. Collip (Fellow), Professor and Head of the Department of Biochemistry at McGill University, Montreal, recently received the honorary degree of Doctor of Laws from the University of Manitoba

STUDENTS among your **DIABETIC** patients will be grateful to **YOU**, Doctor, for telling them about our

SUGARLESS PASTRIES

for social events

Their pleasure and yours is our duty

May we send a food value list?

CURDOLAC FOOD CO.

325 E Broadway

- - -

Waukesha, Wis

ANNALS OF INTERNAL MEDICINE

VOLUME 9

OCTOBER, 1935

NUMBER 4

FURTHER STUDIES ON THE THYMUS AND PINEAL GLANDS*

By L G ROWNTREE, M D, F A C P, J H CLARK, M D, F A C P, A
STEINBERG, B S, A M HANSON, M D, N H EINHORN, M D, and
W A SHANNON, M D,

Philadelphia, Pennsylvania

THE results of our early studies on the biological effects of thymus extract were published in July 1934. In the present communication we wish to present further studies on the thymus gland, up to April 8, 1935, and also the biological effects of pineal extract (Hanson) when administered to succeeding generations with the identical procedure followed in our thymus studies.

FURTHER STUDIES ON THE THYMUS GLAND

Our knowledge of the physiology of the thymus dates from Friedleben in 1858 who found that it was not indispensable to life and was concerned in some way with blood formation, with nutrition and with growth. In 1908 Basch demonstrated that it was concerned with calcification of bone and intimated its importance in the young. Hewer (1915) and Nitschke (1928) have concurred in this idea. An important series of studies were carried on by Klose and Vogt between 1910 and 1914 indicating that thymectomy in young dogs resulted in adiposity, subsequently in cachexia and finally in death. An excellent critical review, together with the results of their own careful experiments, was published in 1919 by Park and McClure. Their results were entirely negative.

On the biological side, Gudernatsch (1913) found that tadpoles grew

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

From the Philadelphia Institute for Medical Research from the Samuel Bell Jr, Laboratory in the Philadelphia General Hospital, the Laboratories of the Philadelphia General Hospital, Philadelphia, Pennsylvania, and the Hanson Research Laboratory, Faribault, Minnesota.

This work was supported by a grant from the Penrose Fund of the American Philosophical Society.

We wish also, to acknowledge with gratitude the financial assistance given one of us, Dr Hanson, by the Josiah Macy, Jr, Foundation.

very large without metamorphosis when they were fed thymus glands Uhlenhuth confirmed these findings but explained them on a nutritional basis Gudernatsch also showed that feeding of thymus glands in rats through several successive generations resulted in large, well nourished offspring Another interesting phase of the study of thymus has to do with eggshells Soli found that thymectomy caused pullets to lay eggs lacking in shells Oscar Riddle, finding pigeons laying eggs without shells, treated them with thymus gland which resulted in the laying of normal eggs Perhaps the most significant work in relation to the biological effect of the thymus gland has been carried on in Asher's laboratory where Victor Nowinski utilized an aqueous extract of thymus called thymocrescin He found that under its influence rats that were losing weight on a low vitamin diet returned to normal weight He concluded that the thymus gland has something to do with growth and also with the size of the gonads

Our experiments were conducted as follows 1 cc of thymus extract (Hanson) has been administered to rats intraperitoneally daily even through the periods of pregnancy and lactation As their offspring reach a suitable age, either prepubertally or maturely, they are mated and likewise injected This has been carried on through succeeding generations and the effect on both parents and offspring noted The results up to and including the fifth generation have already been presented¹ The work has been continued now into the tenth generation In addition we wish to present the results of thymectomy in succeeding generations of parents upon the growth and development of their offspring

The Rate of Growth and Development in the Sixth (F₆) Generation

The sixth generation consisted of 82 rats born to four pairs of fifth generation rats The average birth weight was 5.5 gm (control, 4.6 gm) The ears were open almost invariably on the first or second day (control, 2½ to 3½) Teeth were erupted at one day (control, 8 to 10) Hair appeared at two days (control, 12 to 16) The eyes opened between the second and third day (control, 14 to 17) The testes descended by the fourth day (control, 35 to 40) The vagina opened on the seventeenth day (control, 55 to 62) Seventy-five per cent of the young survived (control, 37.8 per cent) The rate of growth and development in this generation was more rapid than any encountered earlier

The Rate of Growth and Development of the Seventh (F₇) Generation

The seventh generation consisted of 93 rats born to five pairs The average birth weight was 5.6 gm Eighty-four per cent of the young survived The ears were open in some instances on first inspection, only occasionally was this delayed until the first day The teeth likewise were erupted sometimes at birth usually in the first 24 hours Hair appeared as a rule on the first or second day The eyes opened at one and one-half to two days The testes descended from the fourth to the fifth day The vagina opened in every instance by the twenty-fourth day, most frequently from the sixteenth to the eighteenth day One pair of the seventh generation became

pregnant as early as the forty-sixth day and delivered on the sixty-eighth day (Figure 1)

The Rate of Growth and Development in the Eighth (F_7) Generation
The eighth generation consisted of 48 rats born to four pairs. The average

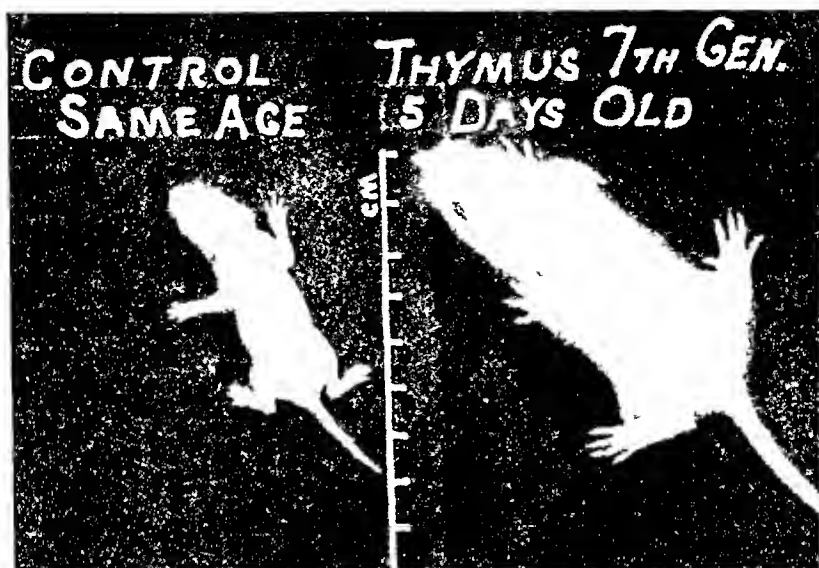


FIG 1

birth weight was 5.4 gm. Ninety-three per cent survived. In this group the ears were open on the first inspection, at six hours or at least within 24 hours. The incisors were erupted as early as eight hours and in every instance on the first day. Hair appeared on the first or second day. The eyes opened as early as 42 hours. The testes descended on the third to the fourth day and the vagina opened on the sixteenth day. One pair became pregnant as early as the thirty-fifth day. Two litters were born under 60 days.

The Rate of Growth and Development in the Ninth (F_8) Generation
The ninth generation consisted of 33 rats born to three pairs. The average birth weight was 6.3 gm. One hundred per cent of the young survived. The ears were open at birth or on first inspection within 24 hours. The incisors were erupted at birth or within 24 hours. Hair appeared on the first day in moderate amounts, the animals being covered with a profuse fur within two days. The eyes began to open as early as 42 hours, and this was completed in every instance but one, in 43 hours. The testes descended on the third to the fourth day and the vagina opened on the sixteenth to the seventeenth day. One of these pairs became pregnant on the twenty-second day and cast a litter on the forty-third day. The mother, four days prior to delivery, weighed 102 gm and after delivery five rats weighed 90 gm.

The Rate of Growth and Development of the Tenth (F_9) Generation

The tenth generation consisted of one litter of eight with a birth weight of 6 gm. Seven young survived. The ears were open and the teeth were present at first inspection. Hair appeared in six hours. The eyes were opened in 36 to 40 hours. The testes were descended by the third day and the vagina was opened on the sixth day, estrus following within three days as shown by smears. The rats of the tenth generation were from the standpoint of every criterion the most precocious observed in the study to date.†

Activity and Behaviorism of Rats under the Influence of Thymus Extract (Hanson) The psychic precocity is as striking as the physical in the thymus treated strain of rats. Thus, rats of the fifth to the tenth generation test strain run about the cage at from two to three days of age and are as alert as normal rats of 16 to 20 days of age. These animals will climb out of a wire net enclosure from 3 to 4 inches high and manifest all the activities of normal animals four or five times their age. Weaning is possible as early as 48 hours, the little rats finding their own supply of water, milk and food. They nest, burrowing under the excelsior, and find a resting place and have no need of further care from the parents. The weaned animals have fared as well, and in some instances better, than their litter mates left with the parents. The thymus treated animals appear to be healthy, contented and docile. Their actions, asleep or awake, resemble those of normal controls in every way.

Rats of the advanced generations can swim as early as the third day. The growth in these generations as in the earlier ones is affected only in the early days of life, more especially before the sixteenth day. Giants do not develop.

It is interesting to note, we believe, that the original pair of thymus test animals are still living after 25 months and that they have lived to see their descendants into the tenth generation.

In the animals of the third to the tenth generations striking and accruing precocity, and acceleration in growth and development, were noted in the offspring of each succeeding generation under treatment. The normal rate of growth and development and the precocity resulting from continuous administration of thymus extract through succeeding generations are shown in the accompanying table (Table 1).

The increasing growth as indicated in weight curves is shown in the accompanying figure (Figure 2).

The Effects of Thymectomy in Successive Generations A study of the effects of thymectomy in successive generations of parents upon the rate of growth and development in the young is being undertaken by Dr. N. H. Enhorn and Dr. W. A. Shannon. The removal of the thymus appears to

* This phenomenon awaits histologic confirmation of findings in the ovary.

† With the original extract the effects on acceleration of growth and development were extremely consistent. Since that supply was exhausted and we have been utilizing batches of thymus extract made up in the Institute there has been more variability especially in relation to weight.

TABLE I
Development of Thymus Treated Rats and Their Controls

	Controls	I ₁	I ₂	I ₃	I ₄	I ₅	I ₆	I ₇	I ₈	I ₉
Aver Birth Wgt (gm)	4.6	5.1	5.3	5.3	5.6	5.5	5.6	5.5	6.5	6.0
Ears Opened (days)	2 ¹ / ₂ -3 ¹ / ₂	2-3	2	1-2	1-2	1-2	2-2	Birth	Birth	Birth
Incisors Erptd (days)	8-10	8-9	4-6	4-6	2-3	2	1-2	Birth	Birth	Birth
Hair Appd (days)	12-16	10-12	4-6	1-6	2-3	2	1-2	1-2	1	1
Eyes Opened (days)	14-17	12-14	4-6	4-6	2-3	2-3	2-3	42-48 hours	42-48 hours	36-42 hours
Testes Descd (days)	35-40	15-29	15-21	10-12	6-10	4-6	3-10	3-4	3-4	2-3
Vagina Opened (days)	55-62	30-45	23-32	21-27	18-20	18-20	16-20	16-18	16-18	6
Pregnant (days from birth)	80	70	56	42	25	40	46	37	22	—
First Litter Cast (days from birth)	102	92	78	64	47	61	68	59	43	—

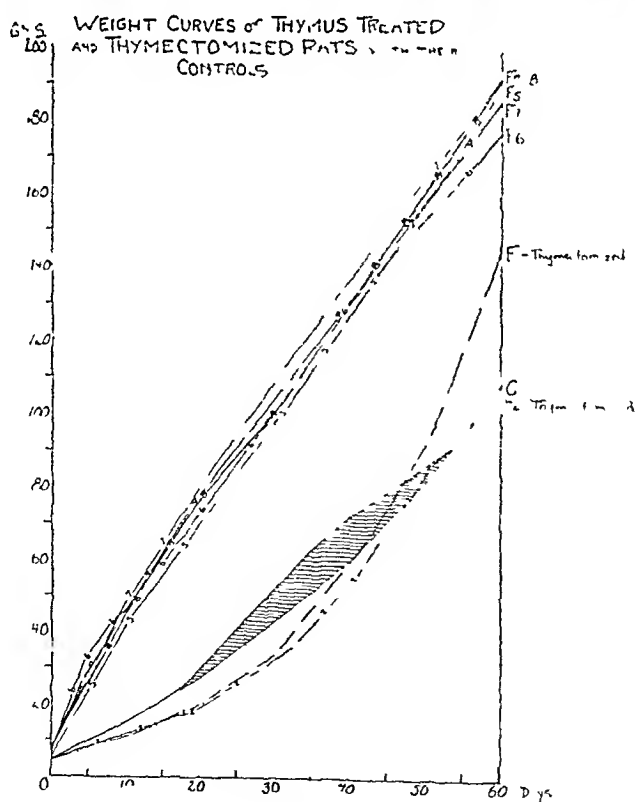


FIG 2



FIG 3

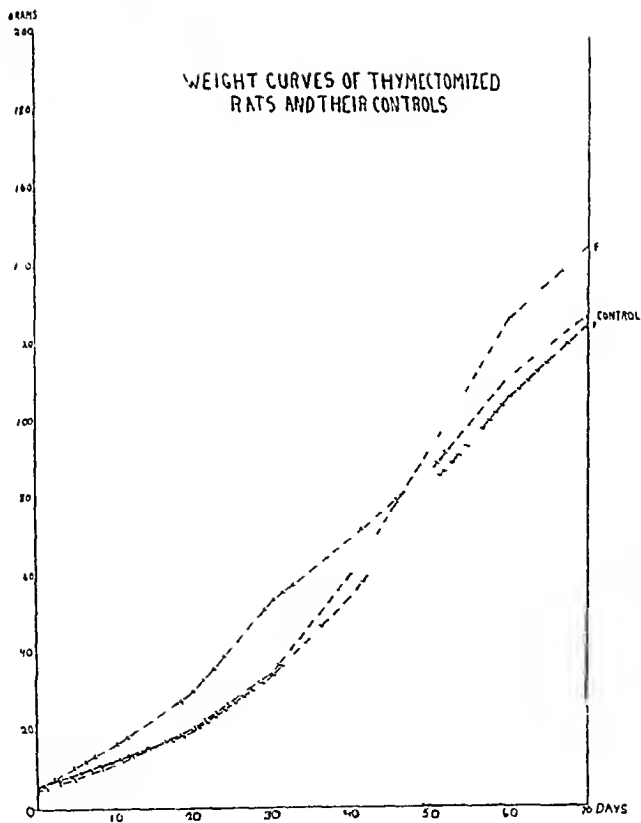


FIG 4

retard growth in the second and third generations but the effect on differentiation is not so striking. In practically all of the young born, the eruption of teeth, the opening of the eyes, the growth of fur, etc., is within normal time but usually at the lower extreme of normal. Thus the eyes open on the sixteenth day, occasionally on the seventeenth or eighteenth day, but at least up to the third generation there is no abnormal retardation in development (Figure 3). The effects on growth as revealed in the weight curves, can be seen from the accompanying figure (Figure 4).

It would appear, therefore, that thymectomized rats are retarded in growth during the first 10 weeks of life, the weight curves lagging below the normal to the extent of 25 to 30 per cent. After maturity the weight curves are essentially normal.

FURTHER STUDIES OF THE PINEAL GLAND

The success attending our studies with the continuous administration of thymus extract (Hanson) to successive generations of parent rats, resulting in the remarkable precocity in the offspring of the third and succeeding generations, led us to attempt the same procedure with an extract of the pineal gland.

Experimental Procedure. A small colony of four pairs of albino rats (Wistar strain) was started on pineal extract on March 2, 1934. Test animals have been subjected to date to 1 c.c. intraperitoneally of pineal extract daily even during periods of pregnancy and lactation. Offspring born to these rats have been mated in pairs and these likewise have been so treated and the effects of pineal extract on parents and offspring noted.

Thus the original test animals of the first generation (F_0) have undergone continuous treatment since March 2, 1934, the second generation (F_1) since April 2, 1934, the third generation (F_2) since September 18, 1934, the fourth generation (F_3) since November 12, 1934, and the fifth generation (F_4) were started on this treatment on March 18, 1935*. In the offspring, treatment was begun, in the prepubertal group, from the sixteenth to the twenty-fifth day and, in the mature group, from the fortieth to the sixtieth day. At the present time we have reached the fifth generation of pineal treated rats and have over 300 such in this colony.

The Nature of the Pineal Extract Used. The pineal extracts which we have employed were made from pineal glands from beef of average killing age. Several such extracts have been prepared, namely P. B. No. 22 to No. 29 inclusive. The most potent of these was found on investigation to be P. B. No. 22. No effects were observed as a result of administering extracts P. B. No. 23 to No. 27 inclusive. P. B. No. 28 and No. 29 are being subjected to assay at the present time. To date, however, none appear to be preferable to the original extract employed, P. B. No. 22. This is a slightly turbid, somewhat greenish looking solution, nonirritating locally and relatively non-toxic to rats in doses of 1 c.c. intraperitoneally.

* In the text, F_0 animals are referred to as first generation and F_4 as fifth generation respectively.

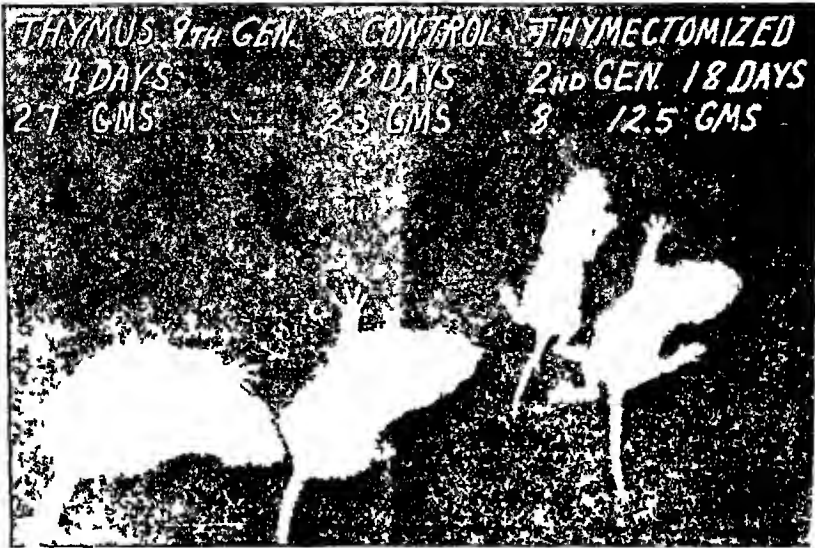


FIG 3

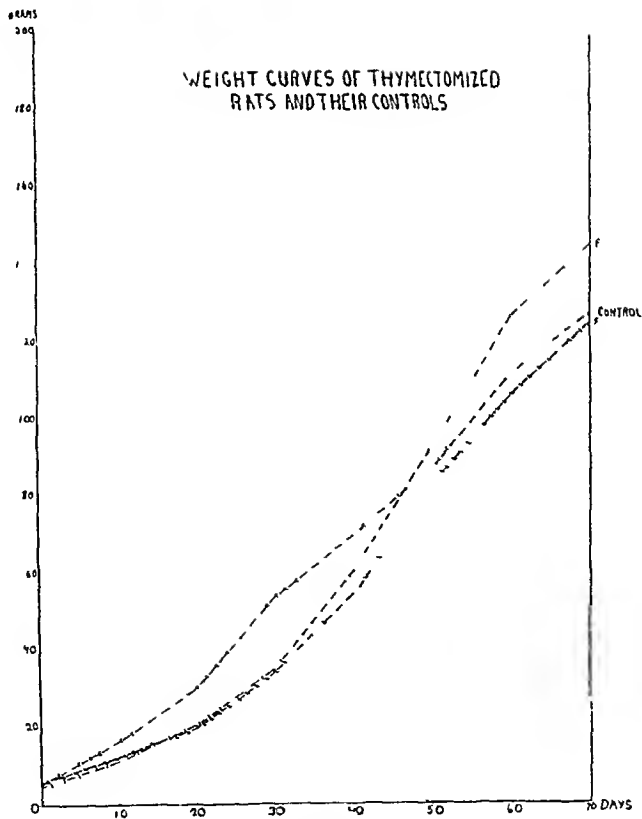


FIG 4

retard growth in the second and third generations but the effect on differentiation is not so striking. In practically all of the young born, the eruption of teeth, the opening of the eyes, the growth of fur, etc., is within normal time but usually at the lower extreme of normal. Thus the eyes open on the sixteenth day, occasionally on the seventeenth or eighteenth day, but at least up to the third generation there is no abnormal retardation in development (Figure 3). The effects on growth, as revealed in the weight curves, can be seen from the accompanying figure (Figure 4).

It would appear, therefore, that thymectomized rats are retarded in growth during the first 10 weeks of life, the weight curves lagging below the normal to the extent of 25 to 30 per cent. After maturity the weight curves are essentially normal.

FURTHER STUDIES OF THE PINEAL GLAND

The success attending our studies with the continuous administration of thymus extract (Hanson) to successive generations of parent rats, resulting in the remarkable precocity in the offspring of the third and succeeding generations, led us to attempt the same procedure with an extract of the pineal gland.

Experimental Procedure A small colony of four pairs of albino rats (Wistar strain) was started on pineal extract on March 2, 1934. Test animals have been subjected to date to 1 c.c. intraperitoneally of pineal extract daily even during periods of pregnancy and lactation. Offspring born to these rats have been mated in pairs and these likewise have been so treated and the effects of pineal extract on parents and offspring noted.

Thus the original test animals of the first generation (F_0) have undergone continuous treatment since March 2, 1934, the second generation (F_1) since April 2, 1934, the third generation (F_2) since September 18, 1934, the fourth generation (F_3) since November 12, 1934, and the fifth generation (F_4) were started on this treatment on March 18, 1935*. In the offspring, treatment was begun, in the prepubertal group, from the sixteenth to the twenty-fifth day and, in the mature group, from the fortieth to the sixtieth day. At the present time we have reached the fifth generation of pineal treated rats and have over 300 such in this colony.

The Nature of the Pineal Extract Used The pineal extracts which we have employed were made from pineal glands from beef of average killing age. Several such extracts have been prepared, namely P B No 22 to No 29 inclusive. The most potent of these was found on investigation to be P B No 22. No effects were observed as a result of administering extracts P B No 23 to No 27 inclusive. P B No 28 and No 29 are being subjected to assay at the present time. To date, however, none appear to be preferable to the original extract employed, P B No 22. This is a slightly turbid, somewhat greenish looking solution, nonirritating locally and relatively non-toxic to rats in doses of 1 c.c. intraperitoneally.

*In the text, F_0 animals are referred to as first generation and F_4 as fifth generation respectively.

In preparing this extract, beef pineal glands were secured at the kill and frozen in dry ice, with as little delay as possible. The glands were ground in their frozen state and each 100 gm transferred to a four-liter beaker of Pyrex glass. Two thousand c c of a 0.1 per cent HCl by volume are then added, the beaker placed over a Bunsen flame on a tripod with asbestos screen, utilizing a mechanical stirrer with a heavy glass stirring rod which is introduced to within $\frac{1}{2}$ inch of the bottom of the beaker. The heating is continued until the temperature reaches 89 to 90° C, when the flame is turned off and 200 c c of an ethyl-methyl alcohol mixture added and the stirring continued for one hour.¹

At the end of one hour, the mechanical stirrer is stopped and the extract filtered through cotton covered with gauze to separate the solution from the solid matter. The extract is then made up to 2,000 c c with boiled distilled water and 1.25 volume of filtered saturated aqueous picric acid added. It is allowed to stand until the picrate precipitate has settled to the bottom of the beaker when most of the supernatant fluid is poured off and the remainder with the precipitate poured on filter paper and allowed to drain over night. The picrate, drained almost dry, but still moist, is removed from the filter paper and transferred to a Pyrex glass beaker of suitable size and extracted in 1000 c c of a 0.25 per cent HCl by volume with constant stirring and heat to 89 to 90° C, made up to its original volume with boiled distilled water and 1 c c of a 91 per cent aqueous solution of phenol added and the extract transferred to a sterile one-liter Pyrex glass flask, capped and cooled to minus 12° C, allowed to stand four hours, or over night, filtered, made up to 1100 c c with boiled distilled water, heated to 89 to 90° C, 4 c c of a 91 per cent aqueous solution of phenol added as a preservative and the extract transferred to sterile 50 c c rubber capped bottles.

Controls Employed The controls were of several kinds: (a) the strain of rats which constituted the controls for our earlier thymus studies, (b) the published data obtained in the study of rats at the Wistar Institute, summarized in *The Rat* by Dr H. H. Donaldson (Cf. table 2), (c) animals injected with 0.21 per cent picric acid solution over a period of several weeks none of which evidenced any demonstrable biologic effects. In our opinion picric acid is definitely eliminated as a factor in the effect observed.

The Effects of Pineal Extract in the First (F₀) Generation Pineal extract has been administered to this group, four pairs of rats, over a period of more than 12 months. While acute toxic effects have not been observed from the small doses employed, the general effect has been one of a mild deterrent to health and growth. All of the surviving animals concerned are now from 450 to 480 days of age. They are decidedly underweight for their present age. In this connection it should be remembered that treatment was begun in these rats when they were mature, at an age of 84 days. In addition the males present some suggestion of an abnormal condition of

* The ethyl-methyl alcohol mixture must be freshly prepared each time and is made up as follows: ethyl alcohol, 95 per cent, 20 c c, and methyl alcohol, synthetic, C. P. 180 c c.

TABLE II
Comparison of Control Rats with Those of the Wistar Institute *

	Strain	
	Wistar Institute	Philadelphia Institute for Medical Research †
No. in litter	6 1	4 9
Ears open	2½ to 3½	2½ to 3
Teeth erupted	8 to 10	9 to 10
Hair appeared	16	12 to 16
Eyes opened	14 to 17	14 to 17
Testes descended	40	31 to 40
Vagina opened	72	55 to 62
Comment	On a varied breeder's diet	On an adequate stock diet

* The measure of time is days

† Based on 104 animals

the external genitalia, enlargement of the penis, possibly priapism or sex excitation and frequently paraphimosis. From the behavioristic point of view these rats appear to be tense and more irritable than normal.

Growth and Development of the Second (F₁) Generation In all, 138 rats were born in the second generation to four pairs of test animals of the first generation under treatment. The biologic data indicate normal and in some cases rapid breeding on the part of the parents, an average period between the casting of litters of 39.6 days for the test animals as compared with 42.5 days for the controls. The average litter consists of 5.1 rats which closely approximates that of our normal controls (4.9). The animals at birth averaged 4.9 gm. which is slightly higher than the normal (4.6). Fifty per cent of the offspring of the test animals survived as compared with 37.8 per cent of the offspring of the controls.

No definite departure from normal was noted in this generation in the earlier litters relative to the opening of the ears, the eruption of teeth, the development of fur, or the opening of the eyes. However, growth was retarded while gonadal development and maturity were somewhat earlier than normal. Also, the penis was enlarged. The testes in all males descended in less than normal time, from 36 to 12 days, at an approximate average of 22 days for the entire group, as compared with the normal (31 to 40). The tendency to early descent is more apparent in the later litters born to the same parents. Thus, in the offspring of No. 500 to No. 501, the testes descended in 31 days in the first litter cast after treatment was begun and in 12 days in the ninth litter (one animal), in the offspring of No. 502 to No. 503 in 26 days in the first and 20 days in the sixth litter, in the offspring of No. 508 to No. 509 in 30 days in the first and in 16 days in the fifth litter. Likewise earlier maturity was encountered in the female, the vagina opening between the fifty-second and the thirty-second day, at an approximate average of 45 days, as compared with the normal of 72 to 55 days.

Variability in the survival rate is worthy of comment. It is rather striking that in the first three litters born to pair No. 500 to No. 501, 100 per

cent survived, whereas in the remaining eight litters, there were but five survivals out of 51 animals. Of the offspring of No 506 to No 507, only five animals survived out of 15 born, all being of the fourth litter. The highest survival was among the offspring of No 508 to No 509, 15 out of 22 animals.

It is interesting also to contrast the first with the tenth litter born to No 500 to No 501. In the first litter cast after treatment was begun all survived and the animals conformed to normal standards throughout except that growth was retarded and the testes descended on the thirty-first instead of the fortieth day, whereas in the ninth litter only 1 of 13 survived and in this rat the teeth erupted at 7 days, hair appeared from the ninth to the eleventh day, the eyes opened at 12 days, the testes descended at 12 days. Mild precocity in hair growth and gonadal development is shown also in the last litter born to pair No 502 to No 503. Hair appeared at 12 to 14 days, the eyes opened at 12 days, testes descended at 20 days (two males only surviving).

Although the birth weight of these rats was normal, growth, as indicated by the weight curves, was decidedly retarded. At 10 days the pineal test strain were at least 25 per cent under normal and at 30 days more than 30 per cent below standard.

The Growth and Development of the Third (F_2) Generation In test animals of the third generation, i.e. animals born to two generations of rats treated with pineal extract, the effect on growth and development was considerable. In all, 543 animals were born in 93 litters to 18 pairs of second (F_1) generation rats under treatment with pineal extract (Hanson). The interval between gestations was 33.8 days as compared with 42.5 days for the controls. An average of 5.6 rats per litter was cast as compared with 4.9 for the controls. The average birth weight was 4.6 gm for the test animals, identical with that of our controls. One hundred and ninety-seven young survived, or 36.2 per cent as compared with 37.8 per cent of the controls. Growth was slow but development rapid. The ears opened from the second to the third day, an average of 2.8 days. The incisors erupted from the seventh to the eleventh day, an average of nine days. The animals were covered with a fine downy fur from the sixth to the seventeenth day, an approximate average of the twelfth day. The eyes opened from the twelfth to the sixteenth day, an average of 13.8 days. The testes descended from the sixth to the twenty-sixth day, an average of 15 days, as compared with 31 to 40 days for the controls. The vagina opened from the thirtieth to the thirty-ninth day, an average of 37 days.

The birth weight in this group was somewhat under that in the second generation and growth was much more retarded. At 10 days the pineal animals lagged by nearly 40 per cent and at 30 days more than 50 per cent. Thus the average pineal rat at one month was less than half the normal size and weight. (Figure 5)

The Rate of Growth and Development in the Fourth (F_3) Generation

The fourth generation consisted in all of 155 animals born in 24 litters to nine pairs of rats treated with pineal extract. The parents, grandparents

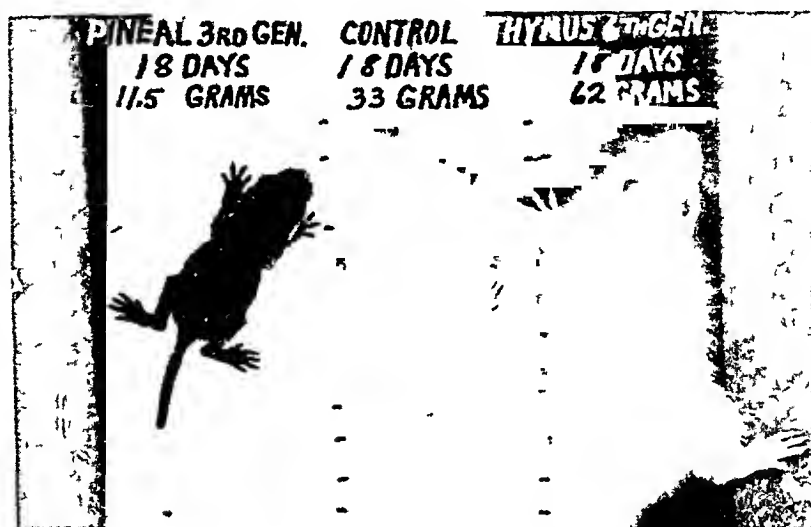


FIG 5 For purposes of comparison the sixth generation thymus rat was included

and great grandparents had all received injections of pineal extract (Hanson). The interval between casting litters was an average of 27.8 days. The average litter consisted of 6.4 animals with an average birth weight of 4.3 gm. The mortality was high, only 30 per cent of the young survived. In this generation growth was still further retarded while development was still further accelerated. The ears opened in two to three days, an average of 2.3 days. The teeth erupted from the fifth to the eighth day, an average of 6.9 days. Hair appeared between the fifth and the twelfth day, an average of nine days. The eyes opened at five to 13 days, an average of nine days. The testes descended at five to 12 days, an average of 10 days, and the vagina opened at 29 to 39 days, an average of 32 days.

The Rate of Growth and Development of the Fifth (F_4) Generation

The fifth generation consisted of 12 rats born in one litter, the birth weight varying from 3.8 to 4.5 gm, an average of 4.2 gm. The two smallest animals succumbed at five days without showing any increase in weight. Ten animals survived for two weeks and only five are living at 30 days. In this group, growth was still further delayed and development still further accelerated. The ears opened on the first to third day. The teeth erupted from the third to the fifth day. Hair appeared from the fourth to the eighth day, was scanty in amount, downy in consistency, the pelt being poor as compared with that of our thymus test strain. The rats opened their eyes between the fourth and the eighth day. The testes descended between the fourth and the ninth day and the vagina opened at an average of 24 days (Figure 6.)

In this generation growth is still further restricted. The weight curve falls below that of the F_1 generation. To attain greater accuracy, we have based this curve on six litters, five of which have been observed since April



FIG 6

16, the closing date for the work as a whole. The rats of the fifth generation weighed 50 per cent of normal at 10 days and those surviving to the thirtieth day weighed but 40 per cent of normal.

General Discussion of the Rate of Growth and Development of Rats under Treatment with Pineal Extract. To date five generations of the pineal strain of rats have been under observation. An analysis of the biological data of each of these generations reveals several significant facts. In the first (F_0) generation no effect is apparent other than a moderate loss of weight, phenomena suggestive of sex excitation or increased size of penis and early breeding. In the second (F_1) generation there is definite retardation in growth with mild precocity in gonadal development. In the subsequent generations, the third to the fifth, there is accruing retardation in growth with accruing acceleration in gonadal and bodily development.

As a result of these changes, the young are quite bizarre in appearance, especially in the second and third weeks until the body is thickly covered with fur. The configuration of the body as well as the shape of the head and the face seem to depart considerably from normal. The short snout, broad face, round head, heavy jowl and bulging eyes give a "bull dog" appearance. The small size, the large feet, the squat, compact figure suggest the "Hercules in miniature" effect said by some to characterize the clinical picture of pineal tumor.

These animals we have referred to as "dwarfs." In this early period the stunting in growth is accompanied by disproportions in bodily development. Later, however, after the first month the animals appear small and

delicate but like normal rats in miniature Still later, after 100 to 200 days, these rats appear somewhat small but normal in appearance but on examination the fur is found to be unusually long and thick and on weighing the animal it is found to be only 50 to 60 per cent of the weight of the control

It is of decided interest that the effect on gonadal development appears earlier than that on bodily development It is quite marked in the second (F_1) generation whereas the precocity in bodily development does not appear until the third (F_2) generation

Lack of uniformity in size and in the rate of growth and development is striking Even in a single litter variation is marked Because of this variability, the range of values as well as the average is presented in the following table (Table 3)

TABLE III
Progressive Development under Pineal Treatment

Controls	Ears Opd	Teeth Erupt	Fur Appd	Eyes Opd	Testes Descd	Vagina Opd
	2½-3½ (3)	8-10 (9 0)	16 16	14-17 (15 5)	31-40 38	55-72 65
F_1	2-3 (3 3)	8-10 (9 0)	7-16 (13 0)	12-17 (14 9)	12-36 (22 0)	32-56 (45 0)
F_2	2-3 (2 8)	7-11 (9 0)	6-17 (12 0)	12-16 (13 8)	6-26 (15 0)	30-39 (37 0)
F_3	2-3 (2 3)	5-8 (6 9)	5-12 (9 0)	5-13 (9 8)	5-12 (10 0)	29-39 (32 0)
F_4	1-3 (2 0)	3-5 (4 0)	4-8 (5 0)	4-8 (6 0)	4-9 (5 0)	23-26 (24 0)

The data on growth and development when tabulated or expressed in curves reveal the same step-like progression in succeeding generations under treatment which was evidenced in our thymus work However, in the pineal studies there appears a peculiar paradox, a dissociation of the effects on growth and development* The progressive effect is in two or possibly three directions, retardation in growth accompanied by acceleration in gonadal development and also in bodily development

The effect of pineal extract on growth is revealed in figure 7, which represents the growth curves of the successive generations † The "dwarf-

* This suggests that more than a single agent or substance is concerned in the process of growth and development Several factors may contribute to this "dwarfism" (1) Loss of weight seen in the F_0 group, (2) retardation of growth by direct effect, and (3) inhibition of growth secondary to gonadal maturity In view of the latter some may not regard the combination of retarded growth with accelerated development as a paradox

† The closing date for these studies was April 16 At that time we had one litter of 12 in the fifth generation on which to base the curve for F_4 It seemed wise to include additional data up to July 4 for both the curves for F_2 and F_4 F_3 is therefore based on 30 litters and F_4 on 5 litters

ism" resulting from pineal extract (Hanson) is usually permanent, though less striking as the animals age. In rats of the second or later generations perhaps less than 10 per cent attained normal weight or growth. The early

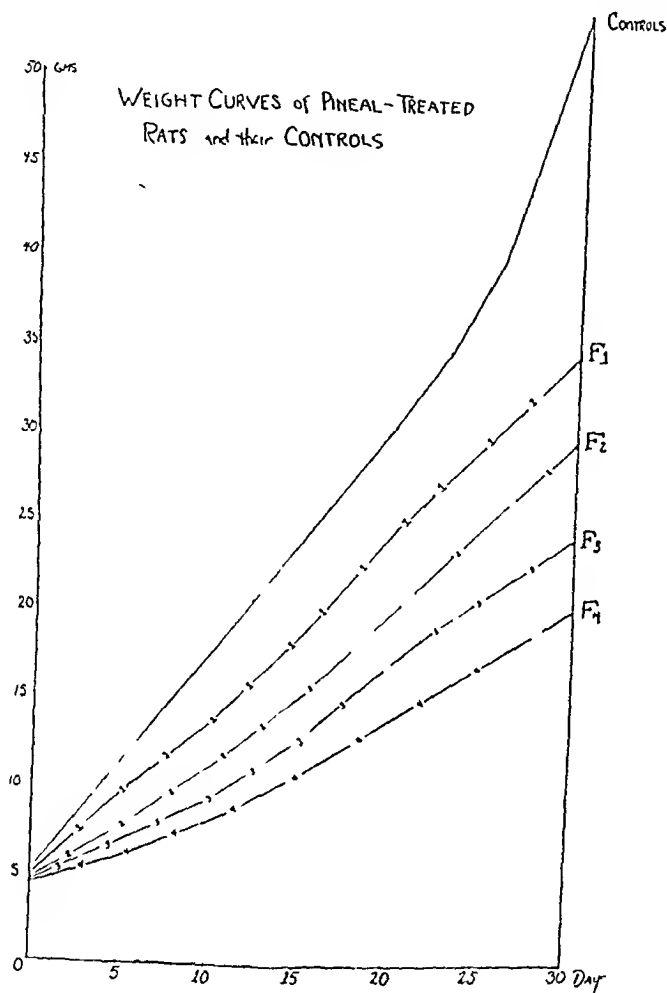


FIG 7

employment of potent extract in the young almost always insures more striking and more permanent effects.

In summary it may be said that on the physical side the biological effect of administering pineal extract (Hanson) is "dwarfism" associated with acceleration of gonadal and bodily development*. It would appear, therefore, that the rats in our third and succeeding generations under pineal treatment in some ways suggest the clinical picture, macrogenitosomia precox, seen in pineal tumor although our animals do not pass through a period of early accelerated growth sometimes encountered in the clinical condition.

* Caution must be exercised in arguing from this statement that a function of the pineal gland is to retard growth and accelerate differentiation since experiments now being carried on in this laboratory by Dr N H Einhorn indicate that pinealectomy also retards growth and is associated with accelerated development.

Other Biological Effects In addition to the effects of pineal extract on the rate of growth and development, certain other considerations appear worthy of presentation. These have to do with activity and behaviorism, time of weaning and the frequency of blindness.

Activity and Behaviorism of Rats under the Influence of Pineal Extract (Hanson) Most of the pineal treated rats appear fairly healthy and their actions asleep or awake resemble grossly those of normal controls although they seem more somnolent or lethargic. However, they are distinctly more irritable than normal. They resent needle puncture though they apparently suffer no undue pain or distress following the injection of pineal extract.

The mother instinct is quite variable, in some instances complete neglect, in others undue apprehension and combativeness to all who even approach the young. At times gloves have been essential in handling pineal mothers when a litter was in the cage, the same animals at other times being friendly and docile.

The young pineal "dwarfs" tend to lie on their side in a curled up position in the first days of life. At this time they are relatively inactive. At the end of the first week, after their eyes have opened they appear weak and have difficulty in getting about the cage. Not until they are 15 to 20 days of age will they attempt to climb the side of the cage or to escape from a small wire net enclosure. Their activity during these early days is decidedly below normal as is their strength.

Weaning Weaning in the early days of life is impossible in the pineal test strain. Even under the best conditions the animals are very small and most of them too weak to wean even at 20 to 23 days of age. When a subsequent litter has arrived in the course of 23 to 25 days, we have found some difficulty in the enforced weaning of the young of the preceding litter. Weaning should be attempted preferably about the thirtieth day.

Swimming Because of their apparent inactivity and helplessness, it was considered inadvisable to immerse very young pineal test rats. However, it has been found that the best developed pineal rats of the fourth and fifth generations can swim at 20 days, most of them, however, not until the thirtieth day.

Eye Anomalies Blindness is of rather frequent occurrence. This has been observed in perhaps a dozen rats in the pineal group but only twice in our thymus strain. As a rule blindness affects one eye but in four instances it has been bilateral. The cause is unknown. It is possible that injury plays a rôle. Bilateral cataracts were responsible in two rats. Two instances of congenital hypertrophy of the eye have been noted² and some instances of the so-called pineal eye.

The opening of the eye is peculiar at times. When the eyelids separate the pupil is not revealed, the slit being too high for the pupil. Eventually, however, some form of adjustment is effected, whereby the eyeball and palpebral fissure appear to harmonize.

CONCLUSIONS

1 Thymus extract (Hanson) has accelerated the rate of growth and development and has hastened the onset of adolescence in the offspring of treated rats

2 Thymectomy in parent rats has retarded the rate of growth in the young as indicated in the weight curves

3 Pineal extract (Hanson) has retarded the rate of growth and accelerated the rate of development and has hastened the onset of adolescence in the offspring of treated rats

4 The injection of succeeding generations of parent rats has resulted in the amplification of the effects of thymus and pineal extracts (Hanson)

We wish to acknowledge our indebtedness and gratitude to Dr H H Donaldson of the Wistar Institute for his kindly interest, unfaltering faith and invaluable counsel

REFERENCES

- 1 ROWNTREE, L G, CLARK, J H, and HANSON, A M The biological effects of thymus extract (Hanson), Jr Am Med Assoc, 1934, ciii, 1425-1430
- 2 ADDISON, W H F, and HOWE, J W Congenital hypertrophy of the eye in an albino rat, Anat Rec, 1926, xxii, 271
- 3 BASCH, K Über Ausschaltung der Thymusdrüse, Verhandl d Gesellsch deutsch Naturf u Aerzte, 1902, Leipsiz Also Wien klin Wchnschr, 1903, xvi, 893-896
- 4 BASCH, K Bemerkungen zu Rudolf Fischl's experimentelle Beiträge zur Frage der Bedeutung der Thymusexstirpation bei jungen Thieren, Ztschr f exper Path u Therap, 1905, ii, 195-198
- 5 BASCH, K Über die Beziehung der Thymus zum Nervensystem, Jahrb f Kinderh, 1908, lxxviii, 668-691
- 6 BASCH, K Zur Thymusexstirpation beim jungen Huhn, Monatschr f Kinderh, 1908, vii, 541-545
- 7 FRIEDLEBLN, A Die Physiologie der Thymusdrüse in Gesundheit und Krankheit vom Standpunkte experimenteller Forschung und klinischer Erfahrung, Ein Beiträge zur Lebensgeschichte der Kindheit, Frankfurt a M literarische Anstalt, 1858
- 8 GUDFRNATSCH, J F Feeding experiments on tadpoles, Am Jr Anat, 1914, xv, 431-480
- 9 HEWER, E E The effect of thymus feeding on the activity of the reproductive organs in the rat, Jr Physiol, 1914, xlvii, 479-490
- 10 HEWER, E E The structure of the thymus gland and of the reproductive organs in white rats together with some observations on the breeding capacity of these animals, Jr Physiol, 1914, i, 434
- 11 KLOSE, H, and VOGT, H Klinik und Biologie der Thymusdrüse mit besonderer Berücksichtigung ihrer Beziehungen zu Knochen- und Nervensystem, Beitr z klin Chir, 1910, lxi, 1-200
- 12 KLOSE, H Über Thymusexstirpation und ihre Folgen, Arch f klin Chir, 1910, xcii, 1125-1141
- 13 NITSCHKE, A Darstellung zweier wirksamer und spezifischer Thymussubstanzen, ihr Einfluss auf Kalk und Phosphatgehalt des Kaninchenserums, Ztschr f d ges exper Med, 1929, lxxv, 637-650
- 14 NITSCHKE, A Die Beeinflussung des Grundumsatzes durch Thymus und Milzextrakt (P Substanz), Monatschr f Kinderh, 1930, xlvii, 530-533
- 15 NOWINSKI, V W Fortgesetzte Untersuchungen über den Einfluss des Thymocrescins auf das Wachstum, Biochem Ztschr, 1932, ccxli, 421-423

- 16 PARK, E A , and McCLURE, R D Results of thymus extirpation in dog, *Am Jr Dis Child* , 1919, *xviii*, 317
- 17 RIDDLE, O , and KRIZENFELY, J Extirpation of thymus and bursa in pigeons with a consideration of failure of thymectomy to reveal thymus function, *Am Jr Physiol* , 1931, *xvii*, 343-352
- 18 RIDDLE, O and FRAY, P Growth and age involution of thymus in male and female pigeons, *Am Jr Physiol* 1925, *lxvi* 413-429
- 19 UHLENHUTH , quoted by HOSKINS *The tides of life*, 1933, W W Norton & Co New York

ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF LOBAR PNEUMONIA¹ †

By BENJAMIN BURBANK, M D , and EMIL ROTHSTEIN, M D ,
Brooklyn, New York

DURING the past year, a number of reports^{1, 2, 3} have been published of effects secured in the therapy of lobar pneumonia by the use of artificial pneumothorax. We present here a report of 20 cases of lobar pneumonia treated by artificial pneumothorax, with a resulting mortality of 10 per cent. We realize that no permanent conclusions can be reached from such a small series, but we feel that until larger and more carefully controlled groups of cases have been reported it is important to make available all data bearing upon the effect of this mode of treatment. We wish also to present certain views of our own as to the rationale of this therapeutic procedure.

Selection of Cases We have treated, in this series, 20 cases, selected only by the indications and contraindications stated below. The total number of cases which were available made it seem inadvisable to treat alternate cases, as we then would have had an insufficient number of treated cases. We have no controls, the only cases with which any comparison could be made are seven patients in whom the proper indications existed but no free pleural space could be found, or a pleural effusion was present. Similarly, because of the small number of cases treated, we feel it unnecessary to compare the statistical results with those for the hospital as a whole in previous years. There can be no doubt that if in a much larger series, including all or any types of pneumococci, a mortality of 10 per cent were not exceeded this would represent a marked improvement in pneumonia mortality statistics, especially for a city hospital of the nature of Kings County Hospital, receiving as it does, the indigent, the overexposed and the alcoholics.

The essential data on our 20 cases are given in table 1. We have selected four case abstracts to illustrate the varying therapeutic effects.

CASE REPORTS

Case 3 N W, Jewish male, age 42, was admitted on October 28, 1934. He had been taken ill with pneumonia on the day before admission. On examination he was found acutely ill, his general condition was poor, temperature 104° F with proportionately elevated pulse and respirations. Dyspnea was well marked with rapid shallow respirations due to marked chest pain. There was evidence of complete consolidation of the right lower lobe. No complications were present. Pneumothorax was started October 29, with 350 c c of air, followed that afternoon by 350 c c more, and by 300 c c the following morning, the final pressure going to plus 4 cm. of

* Received for publication March 15, 1935.

From the Services of Drs. B. A. Fedde, H. Feinblatt, and J. G. Terrence, Department of Medicine, Kings County Hospital, Brooklyn, N. Y.

† We are deeply indebted for the advice and assistance of Drs. Fedde, Feinblatt and Terrence, and for the permission to report these cases from their services, of which they are, respectively, the Attending Physicians.

TABLE I
Treatment of Pneumonia by Artificial Pneumothorax

Case	Sex	Race	Age	Result	Day of first treatment	Condition at start of treatment	Total amt air injected	Day of disease when temp first reached normal	Complications before treatment	Complications after treatment
1	f	col	28	recov	3	fair	1 600 c c	7th	pregnancy	none
2	m	col	37	died	4	poor	1 000 c c	died	chr alcoholism luectic aortitis	delirium tremens
3	m	w	42	recov	3	poor	1 000 c c	4th	none	none
4	m	w	28	recov	5	poor	800 c c	—	none	bilateral parotitis
5	m	col	45	recov	4	fair	750 c c	—	arterioscl car diovasc dis	empyema au ricular fibrill and flutter
6	m	w	32	recov	4	fair	900 c c	6th	aortic regurgi tation	none
7	m	col	32	recov	2	fair	800 c c	—	none	empyema
8	m	w	34	recov	6	fair	1 050 c c	7th	none	none
9	m	col	25	recov	6	fair	1 350 c c	8th	none	none
10	m	w	27	recov	3	poor	900 c c	7th	none	contralateral spread to r l l
11	m	col	25	recov	5	poor	600 c c	7th	none	none
12	m	col	50	recov	5	poor	900 c c	7th	none	none
13	m	w	52	died	3	poor	500 c c	died	none	contralat spread to en tire left lung
14	m	w	53	recov	4	bad	800 c c	8th	none	none
15	m	w	25	recov	2	poor	1 000 c c	7th	none	none
16	m	w	49	recov	4	poor	1 000 c c	10th	none	carbuncles
17	m	w	44	recov	5	fair	1 000 c c	7th	none	none
18	m	col	25	recov	4	fair	1 000 c c	5th	none	none
19	m	w	62	recov	3	poor	600 c c	8th	none	none
20	m	col	42	recov	1	poor	700 c c	3rd	congenital heart disease	none

water The immediate effect was an increase in pain, this lasted for 20 minutes and then was followed by complete and permanent relief of pain. The patient became much more comfortable and slept peacefully through the afternoon and the following night. He was able to breathe deeply and cough without pain. On the afternoon of October 30 (the middle of the fourth day) the temperature dropped to 99° and remained normal from then on.

Case 2 P W, negro male, age 37, was admitted July 2, 1934. The onset of his pneumonia had been on June 29, 1934. On admission his examination showed that he was acutely ill and in poor general condition. His temperature was 103° F, and there was a proportionate rise in pulse rate and in respirations. Dyspnea was well marked with rapid shallow respirations due to moderate chest pain. The lung involvement found consisted of complete consolidation of all three lobes of the right lung. In this patient certain complications were present: luectic aortitis (asymptomatic and found at postmortem), and chronic alcoholism. The first pneumothorax treatment (300 c c) and the second (400 c c) were given on the day of admission and the third treatment (300 c c) on the day following, July 3. The final pressure was plus 2 cm of water. Immediately after the first treatment the patient had complete and permanent relief of pain. A few hours after the first treatment he showed evidence of beginning delirium, four hours after the second, a full-blown delirium tremens was present, requiring sedation and restraints. In addition to pneumothorax, he received oxygen inhalations, and intravenous glucose. Death occurred on July 3, 1934. Autopsy revealed consolidation of the entire right lung, cerebral edema and luectic aortitis.

Case 4 T L, Greek, male, age 28, was admitted November 3, 1934, on the fifth day of his pneumonia. On examination he was found acutely ill, but his general condition was fair. His temperature was 103° F, with commensurate increase of the

pulse and respirations. Dyspnea was moderate, with moderate chest pain. The lung involvement found consisted of consolidation of the left lower lobe. No complications were present. Pneumothorax was started November 4 with 400 c.c., on November 5 400 c.c. more were given. Immediate and complete relief of pain was obtained.



FIG. 1. *Case 3*. Plate taken on admission, complete consolidation of the right lower lobe.

and he was able to breathe, cough, and sleep without difficulty. That afternoon, consolidation of the right lower lobe was discovered, the general condition became poor and required the use of an oxygen tent and intravenous glucose. When his pneumonia was just beginning to resolve he developed bilateral parotitis, that on the left side required incision and drainage. He was discharged as recovered on December 20. It is of interest to note that the left side was completely resolved and aerated within three weeks of the onset, while the right, untreated, took six to seven weeks to become completely resolved (as determined by roentgen-ray).

Case 20. G. D., negro male, age 42, was admitted December 27, 1934. There was a history of some heart condition since the age of two. The onset of his pneumonia was on the day of admission. The examination on admission showed that he was acutely ill but without pain or dyspnea. His heart was enlarged and there was a loud systolic basal murmur. There was no apparent cyanosis and no other evidence of past or present decompensation. This cardiac condition was interpreted as due to congenital heart disease. The roentgen-ray of the heart revealed enlargement and

marked prominence of the pulmonary conus. Examination of the lungs showed complete consolidation of the left lower lobe. Pneumothorax was started on December 28, 1934 (20 hours after the onset). At the first treatment 300 cc were given and the same afternoon 400 cc more, the final pressure going to plus eight cm of water. There was no notable symptomatic effect. The temperature dropped to



FIG. 2. Case 3. After the introduction of 1000 cc. Air is seen between the involved portion of the right lung and the chest wall, and the lung and the diaphragm. The upper portion of the right lung is adherent.

normal on the afternoon of December 29, i. e. 50 hours after the onset of the disease, and remained normal. This is the only case in which the early crisis may be attributed to the treatment. This may be related to the early start of the treatment in this case.

Indications and Contraindications. In the present state of our knowledge it is only possible to define indications and contraindications tentatively. For the present we have set for ourselves certain arbitrary indications with the realization that as time goes on they may become either more elastic or more rigid. With these reservations we list the indications that have guided us in this series.

- 1 The pneumonia must be of the lobar type
- 2 The lung involvement must be unilateral
- 3 The age of the patient must be below sixty
- 4 Moribund patients must be excluded
- 5 The patient must be actively febrile
- 6 The stage of the disease must be earlier than the sixth day
- 7 Pleural effusion must not be present
- 8 Complications already present must be considered



FIG 3 Case 2 Plate taken after the introduction of 1600 cc of air The total amount of consolidated lung is unchanged The apparent collapse is due to two factors (a) the cardiac displacement, (b) collapse of the uninvolved portion of the right lung

Lobar Pneumonia Because of certain pathological features, chiefly pleural involvement and a tendency to be unilateral, as well as the tendency to run a short and acute course, lobar pneumonia is more suitable for pneumothorax treatment than is bronchopneumonia To date we have treated only cases of lobar pneumonia

Unilateral Lesion All our cases were selected as unilateral, in some, physical signs were misleading, and roentgen-ray evidence was relied upon After pneumothorax was started, three cases developed lobar contralateral

lesions, one of these died and two recovered. In addition, in several cases small infiltrative patches were seen on the roentgen-ray, on the previously unaffected side, with neither signs nor symptoms, nor noticeable effect upon the course. Although no bilateral cases were treated deliberately, from our experience to date it does not seem likely that any ill effects would ensue,



FIG 4 *Case 20* This illustrates the congenital heart condition. A small area of pneumothorax is seen in the left lower lung field. The left lung is almost completely resolved. A small patch of pneumonic involvement is seen in the right mid-field.

if this treatment were cautiously used, in a bilateral lobar pneumonia, especially in the presence of severe pleuritic pain. Of our cases, at the onset of treatment, nine had consolidation of the left lower lobe, four of the right lower lobe, two of the right lower and middle lobes, two of the entire right lung and one each of the right upper lobe, of the right middle and upper lobes, and of both lobes of the left lung.

Age The principal factor to be considered here is the function of the lungs, as affected by the presence of emphysema and chronic bronchitis. These pulmonary conditions increase with increasing age. We have arbitrarily set 60 years as the upper limit, but we pay less attention to the

chronological age than to the presence of diminished breath sounds, fixed barrel chest, numerous rhonchi, and a past history of dyspnea upon slight exertion. In the absence of these factors we would at present not hesitate to treat a patient above the age of 60 (as in our case 19). With such patients it is advisable to give small amounts of air, and cautiously. Of our cases, six were in the third decade, four in the fourth, six in the fifth, three in the sixth, and one in the seventh (62), with an average age of 40 years.

General Condition Moribund patients no longer would respond to pneumothorax, because this form of treatment does not directly affect the immunologic balance. One case which we attempted, but in which there was no free pleural space, died 16 hours after the attempt at pneumothorax. The general condition of our patients on the day of treatment was estimated as fair in eight cases, poor in eleven, and bad in one.

Fever For proper evaluation of statistical results no cases should be treated unless acutely ill and febrile, because otherwise cases will be included after the crisis with signs of consolidation still present, thus falsely increasing the percentage of recoveries. From a therapeutic standpoint there is probably no contraindication. All our cases were actively febrile (temperatures of over 102° when treatment was started).

Day of Illness Cases febrile past the sixth day are not suitable for treatment while pneumothorax is still in the experimental phase, as a large percentage of such cases if uncomplicated will recover. From a therapeutic standpoint there is probably no contraindication, and indeed, pneumothorax may be indicated if there is definite evidence of prolongation of the fever due to lobal contralateral extension. Of our series, treatment was started during the first day in one case, the second day in two, the third day in six, the fourth day in five, the fifth day in four, and the sixth day in two, an average of three and one-half days.

Pleural Effusion From a therapeutic standpoint, cases with small effusions probably do not offer any contraindications, but until the percentage of empyemas with pneumothorax treatment is established it would not be wise to treat cases with this complicating factor.

Complications already Present At the start several of our patients had various complications. Our first patient was pregnant (two months). Our second patient was a chronic alcoholic, this condition progressed to delirium tremens and proved to be a fatal complication. This patient had also (as shown at autopsy) luetic aortitis. Our fifth patient (52 years old) had arteriosclerotic heart disease, and during the course of the pneumonia he developed auricular fibrillation followed by auricular flutter (EKG), clinically we also found partial block and pulsus alternans. Our sixth patient presented a cardiac condition, with signs of aortic regurgitation, but without cardiac enlargement, or any signs of past or present decompensation. The Wassermann was negative. Our twentieth case presented a congenital cardiac condition, probably tetralogy of Fallot (loud systolic rumble over

the pulmonic area, cardiac enlargement, marked enlargement of the pulmonary conus in the roentgen-ray, no cyanosis or evidence of past or present decompensation, history of heart disease since the age of two) None of these complications was thought to be sufficient to contraindicate the use of pneumothorax, and the outcome of these cases bore out this opinion

Method of Treatment Our selection of cases was guided by the indications and contraindications discussed above We found it advisable in doubtful cases to take a roentgen-ray, before treatment

The apparatus utilized was the standard pneumothorax machine, with 18-20 gage needles, no special needles were used When feasible, the site of puncture was selected over one of the uninvolved lobes Novocaine anesthesia was used Air was never introduced until the fluctuations obtained were characteristic of intrapleural pressures Readings were taken frequently to avoid sudden pressure rises The amounts introduced in our cases varied from 200 to 500 c c for one treatment and a total of 600 to 1600 c c At present we feel that the ideal amount is about 1000 c c, divided into two treatments of 500 c c each, at a four to six hour interval Most of the patients were benefited greatly by the first 500 c c, and none of those receiving over 1000 c c were noticeably harmed

Pressure Readings and Amounts The initial readings found will vary, but the average is slightly less negative than in the normal chest, assuming the normal to be -10 to -6 cm H_2O , our cases average about -6 to -2 cm Two or three cases had higher negative readings (-14 , -10) and others less negative (-4 , 0) In all cases, after 500 to 1000 c c, the pressure rose much more than in normal or slightly diseased lungs (as in tuberculosis) Arbitrarily we set as the limit of positive pressure, plus 10 cm of water, although we prefer, if possible, not to reach such pressures When the pressures rise rapidly, we prefer to divide the course of treatments into doses of 250 to 300 c c, rather than 500 c c However, there was no discernible relationship between the degree of comfort, dyspnea or relief of pain and negativity or positivity of the intrapleural pressures Therefore we are much less reluctant to go to pressures of plus 6 or plus 8 if necessary, than when we first started this series of cases

Clinical Effects These may be divided into immediate and delayed *Immediate effects* None of our cases presented any immediate pain, shock or discomfort Upon introduction of the air the immediate effect depends largely upon the previous symptoms In the presence of severe pleural pain, the relief is immediate and almost complete, occurring while the air is still being administered The patient is changed from one who is in pain, breathing with short jerky respirations, to one who is comfortable and without pain, and who can breathe and cough freely The subjective relief in these cases is most gratifying In several cases the patient, having been awake most of the previous night due to pain, fell asleep a few minutes after the completion of the first treatment In six cases the treatment caused a small bout of coughing lasting from three to five minutes Four patients

who had no pain before the treatment complained of pain for 10 to 15 minutes afterwards. In no case did this pain last longer, and in all was followed by complete relief of pain. *Delayed effects* (1) Relief of pain is permanent, usually after 500 c c. Relief after the first treatment occurred in 10 cases, after the second treatment in six more, and four had no pain at any time. (2) The effect upon cough. The patient is able to cough freely and without pain, the amount of sputum is increased at first due to the free painless coughing, during the rest of the illness the sputum is apparently less tenacious. (3) The effect upon sleep and rest. The patient is able to sleep and rest without opiates. (4) Distention. None of our 20 patients developed abdominal distention. This is probably directly related to the therapy, and not coincidental, as many of our patients who appeared very toxic were free of this frequent and distressing symptom. (5) Effect upon toxicity. No direct effect was observed. (6) Early crisis. Only two of our cases had a crisis before the fifth day after the onset of the pneumonia (one on the fourth and one on the second day (48-50 hours)). This is different from the experience of the few other physicians who have thus far reported their results with artificial pneumothorax.

Complications These may be divided into immediate and delayed. *Immediate* There were no immediate complications, such as pleural shock, air embolism or increase in dyspnea or cyanosis. *Delayed* (a) Pleural adhesions. Out of 27 cases tried, seven had such diffuse pleural adhesions that either no free space was found or only 75 to 100 c c. of air could be introduced with pressures going up to +10. In these cases pneumothorax was discontinued, and they were considered as not having been treated with pneumothorax. Partial adhesions were present in several cases, frequently over the uninvolved areas. There was no appreciable effect in lessening the efficiency of the pneumothorax, but there were observed somewhat higher pressures than in the other cases. (b) Empyema. Of our 20 cases, two developed empyema. Both were operated upon (rib resection and open thoracotomy) and are gradually recovering. Both were due to *Streptococcus hemolyticus*. The suggestion has been made that those empyemas which would complicate pneumonias with pneumothorax might be expected to be more severe and to have long drawn out courses, because of the effect of the pneumothorax in preventing early encapsulation and localization of the infections. The two patients who developed empyema in our series have been in hands of the surgeons for two and one-half to three months. Whether this will be a constant factor cannot be determined as yet. It is not mentioned in the literature. From a purely hypothetical standpoint one would expect the incidence of empyemas to decrease, as the air removes to a large extent the irritating friction between the two acutely inflamed layers of the pleura. (c) Delayed pulmonary changes. Atelectasis and pulmonary fibrosis have not been observed in any case, the lung being completely expanded in every case before discharge. This absorption takes from two to three weeks. In two cases in which spread to the other side

occurred with later recovery, the lung on the side of the pneumothorax showed much earlier and more complete resolution (roentgenologically) than the other (d) Delirium developed in five cases, in three it required restraint (e) Other complications Delirium tremens developed in one case of chronic alcoholism This patient died Our fourth case developed bilateral parotitis, one side requiring incision and drainage Our fifth case developed auricular fibrillation and auricular flutter, on the basis of a previously existing arteriosclerotic heart disease After a period of seven to ten days during which he was critically ill, he recovered a normal sinus rhythm, he received digitalis, sedation and intravenous glucose This patient also was one of the two who developed empyema Our sixteenth case developed several carbuncles over the sacrum but recovered (f) Three cases developed contralateral lobar pneumonia, one of these died

Results Out of the 20 cases, 90 per cent recovered The mortality in any large group of pneumonias, including all ages, complications and pneumococcus types, ranges considerably over 10 per cent, especially in a hospital of the nature of the Kings County Hospital Although a series of 20 cases is too small for definite conclusions, the mortality of 10 per cent in a series treated from the end of October through December and including nine negroes, is very suggestive In seven cases pneumothorax was tried but no air could be given because of pleural adhesions or effusion Of these, four died, and four developed empyema (including two of the fatal cases)

Rationale of Therapy From our observations of these cases we have come to the following conclusions The beneficial effects of pneumothorax are apparently related only to the relief of pleural irritation There is practically no collapse as seen on the roentgen-ray of the involved lobe and no noticeable effect upon toxicity, nor is it reasonable to assume a diminution of blood or lymph drainage from the involved areas The rationale of the therapeutic effect appears to us to be as follows (a) Effect upon respirations Respiration becomes free, painless and of increased depth This lessens the exertions of the patient, lessens the cyanosis and anoxemia and lessens the chance of contralateral diminished aeration with atelectasis and secondary pneumonic involvement (b) Relief of pain This allows the patient to rest comfortably, sleep is made possible without the use of opiates (c) Effect upon cough Cough is made almost painless in a large majority of the cases, and productive cough insures proper drainage from the diseased area, and also makes much less likely the development of bronchial obstruction in the healthy lobes of the diseased lung or of the opposite healthy lung Such bronchial obstruction with tenacious sputum tends to secondary pneumonic spread (d) Effect upon distention None of our cases developed abdominal distention Inasmuch as this was not apparently related to the lessening of toxicity, we feel that a large part in the development of this troublesome symptom is played by diaphragmatic pleurisy Roentgen-ray studies showed air between the lung and the

diaphragm in almost all cases, and the relief thus afforded at this point is, we feel, directly connected with the absence of distention

Roentgen-Ray Findings All cases were roentgen-rayed at some time in the course of their stay in the hospital and in almost all cases there were several roentgenograms. Only one showed unquestionable collapse of the diseased area. In the other cases, when collapse of the consolidated area was suggested by the film it could be explained by one of three factors: (1) Displacement of the mediastinum, or of the lung into the mediastinum, (2) Collapse of that portion of the lobe which was not completely consolidated, (3) Taking of the film after resolution had begun. The typical picture showed a layer of air (about 1 cm. in width) between the consolidated lung and chest wall, and between the diaphragm and the lung, in lower lobe lesions. The air tended to have a selective location over the diseased, rather than over the healthy, lobes. The air was apparently absorbed by the end of 10 to 14 days. A small amount of fluid was commonly seen in the costophrenic sulcus (in about 50 per cent of the cases).

Comparison with Other Forms of Treatment We do not wish to indicate it as our belief that pneumothorax is meant to replace other accepted forms of treatment, such as serum, oxygen, intravenous glucose, and careful routine nursing and medical care. These forms of treatment should be combined according to the indications and contraindications for each. In this series no serum was used, but oxygen was administered in two of the non-fatal cases, as well as in both of the fatal ones, the indication being the presence of more than the faintest discernible trace of cyanosis. Similarly intravenous glucose (50 c.c. of 50 per cent solution every four hours, for from two to four injections) was administered to six cases, the indication being a drop of blood pressure below 100 systolic.

In comparison with serum, pneumothorax presents certain obvious advantages and disadvantages. Pneumothorax requires no typing, it can be used at once, it is not limited by the pneumococcus type, there is no danger of anaphylaxis. It has also the advantage of being inexpensive. It requires, however, special apparatus and special technical experience. On the other hand, the use of serum is not restricted by age, it can be used in bilateral cases, it is specific, it can be administered by one who has very little experience in such a form of treatment. It is often prohibited, however, by lack of facilities for typing, by the lack of serum for the specific type of pneumococcus, or by economic difficulties. It seems apparent that these modes of treatment are supplementary to each other.

SUMMARY

Twenty cases of lobar pneumonia treated by artificial pneumothorax are reported, with a mortality of 10 per cent. The indications, contraindications, details of treatment, clinical effects, complications, and rationale of pneumothorax treatment are discussed. We believe that artificial pneumo-

thorax is a beneficial method of treatment in lobar pneumonia and should be given more extensive trial

BIBLIOGRAPHY

- 1 LIEBERMAN, L M, and LEOPOLD S S Therapeutic pneumothorax in experimental lobar pneumonia in dogs Am Ir Med Sci 1934, clxxxvii, 315-330
- 2 BEHREND, A, and COWPER, R B G Artificial pneumothorax in treatment of lobar pneumonia, Jr Am Med Assoc, 1934, cli, 1907-1913
- 3 HINFS L E and BENNETT D Artificial pneumothorax in treatment of acute lobar pneumonia Arch Int Med 1935, lx, 100-111

IMMUNOLOGICAL APPLICATIONS OF PLACENTAL EXTRACTS, EFFECTIVENESS BY ORAL ADMINISTRATION †

By C F MCKHANN, A A GREEN, L E ECKLES, and J A V DAVIES,
Boston, Massachusetts

A NUMBER of investigators have found that the umbilical cord blood of infants contains certain antibodies in amounts commensurate with those in the maternal blood stream¹ This would indicate that the immunity of the newborn infant to some of the infectious diseases is derived in part by placental transmission of antibodies from the mother Protein extracts composed of the globulins derived from the human placenta and the blood contained in it have been prepared and have been demonstrated to contain diphtheria and scarlet fever antitoxins, and antibodies which neutralize poliomyelitis virus and protect exposed, susceptible children against measles²

In the present communication we desire, first, to review the progress which has been made in studies to determine the practicability of immunological application of placental extracts, particularly in the prevention and modification of measles, and second, to report investigations which indicate that the immune bodies of placental extracts may be effective following oral administration The tests of the material following oral administration have been made largely by the determination of immunity to scarlet fever as measured by the Dick test

DISTRIBUTION OF ANTIBODIES IN FRACTIONS OF PLACENTAL EXTRACTS

In the preparation of placental extracts, normal placentas from non-syphilitic and non-toxic mothers were collected in sterile containers and were pooled in lots of eight to 50 placentas The organs were ground in a meat chopper and extracted with 4 per cent salt solution The saline extracts contained fetal blood, placental tissue proteins, and some maternal blood After the saline extracts had been centrifugated to free them of blood cells and tissue debris, the globulins were separated by precipitation with half saturated ammonium sulphate The ammonium sulphate was removed by dialysis The preparations so made contained antibodies in considerable concentrations, but the material was in turbid suspension and could not be passed through Berkefeld filters Subsequently a separation of the extracts into fractions was made and the association of antibodies with the various globulins was sought, in order to find, if possible, fractions useful clinically

* Read in part at the Philadelphia meeting of the American College of Physicians, May 1 1935

From the Department of Pediatrics, Harvard Medical School, the Department of Communicable Diseases, Harvard School of Public Health, and the Infants' and Children's Hospitals, Boston, Mass

† The investigations reported herein were supported by a grant from the Commonwealth Fund of New York

which could be passed through Berkefeld or Seitz filters. Also, a series of tests was made to ascertain roughly what proportion of the protein represented blood serum and what was derived from the tissues. In these tests, placentas passed through a meat chopper were placed in cheesecloth bags and all the fluid was drained off insofar as possible. This first fraction was called placental serum although it undoubtedly contained some extracellular tissue fluids. The material was then extracted several times with salt solution and centrifugated in a basket centrifuge. After these extractions the material remaining was again extracted several times with salt solution rendered slightly alkaline. In figure 1 is shown the proteins

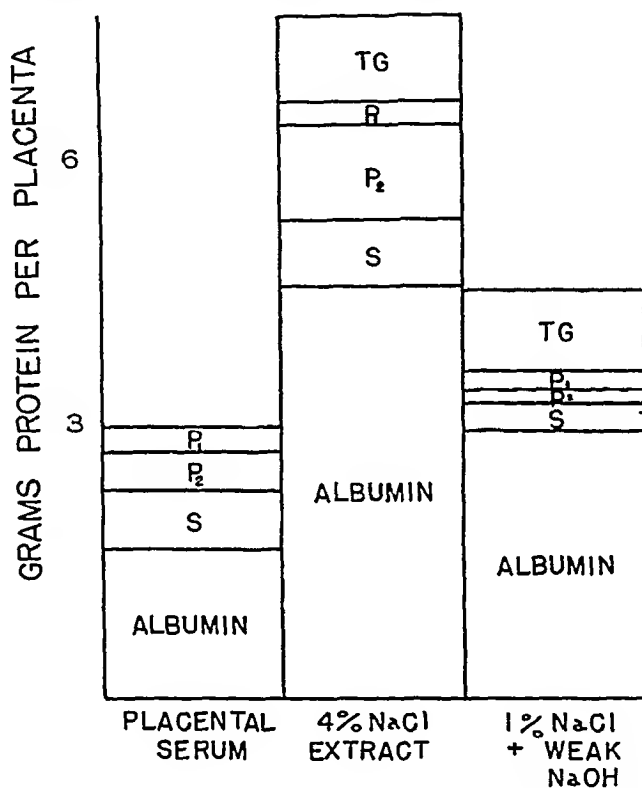


FIG 1 Amounts and types of proteins obtained in successive extractions of placentas

obtained by these three successive types of extraction. It is to be noted that the amounts of protein obtained were considerably greater when the organ was extracted with salt solution or alkalinized salt solution than when the serum was allowed to drain out of the ground tissue.

In the separation of the various proteins from the successive extractions, a combination of the salting out processes and of isoelectric precipitations was finally adopted as more satisfactory than either method of separation alone. Nevertheless the separation of the individual fractions was not complete inasmuch as some overlapping of fractions occurred. Fraction S represented largely pseudoglobulin, while fractions P₁, P₂ and TG repre-

sented euglobulins, the last probably derived from the placental tissues inasmuch as it was present in negligible amounts in placental blood serum. For immunologic tests, the same protein fractions from the separate extractions were usually pooled.

Determinations of the association of different antibodies with the various globulin fractions showed that the diphtheria and scarlet fever antibodies were present only in the more soluble globulins (fractions S and P₁) while the measles and poliomyelitis antibodies were present in all fractions—poliomyelitis certainly and measles probably—even in the large molecule globulins derived from tissue proteins, 1G. This was thought to indicate an association of the immune substances active against the virus diseases, poliomyelitis and measles, with tissue proteins, as well as with blood proteins, in contrast to scarlet fever and diphtheria antitoxins which were not demonstrable in some of the tissue proteins.

USE OF PLACENTAL EXTRACTS IN PREVENTION AND MODIFICATION OF MEASLES

The most extensive clinical trial of the globulin extracts has been in the prevention and modification of measles. For this purpose more than 1300 children have received injections of the extract. The results are shown in table 1. The material used in these studies represented the above mentioned fractions alone as well as in further subdivisions or in combinations. The derivation of the fractions is indicated in the table.

TABLE I
Placental Extract for Prevention or Modification of Measles, Intramuscular Injection

Solution or Fraction		Cases	Protection		Modification		Failure	
T	(0-50)	214	170	79.5%	39	18.2%	5	2.3%
M	(28-50)	415	294	70.8%	95	22.9%	26	6.3%
R	(28-50)S	99	82	82.8%	12	12.1%	5	5.1%
S	(0-50)	201	135	67.1%	60	29.9%	6	3.0%
P	Iso P	100	59	59.0%	31	31.0%	10	10.0%
FP		37	22	59.3%	14	38.0%	1	2.7%
V	(S-TG)	22	12	54.5%	10	45.5%	0	0
W	(T-TG)	6	4	66.6%	2	33.3%	0	0
Total		1094	778	71.1%	263	24.1%	53	4.8%
Commercial Extract		247	181	73.3%	58	23.4%	8	3.2%
Total Cases		1341						

Collected statistics of the use of adult immune serum and of convalescent serum in comparison with the results obtained by the use of placental extract are shown in table 2.⁴ Obviously criticism of these results can be made because they represent all types of exposure and doubtless include many cases which were not actually infected with the disease. We have taken cog-

nizance of this fact and have subjected the results obtained in the use of placental extract to a more rigid test by excluding cases exposed in institutions or at play, unless the development of measles indicated that they

TABLE II

Patients Treated for Prevention or Modification of Measles with Adult Serum, Convalescent Serum and Placental Extract

Procedure	Number of Cases	Protected		Modified		Failed	
Adult Serum	584	329	56.4%	139	23.8%	116	19.8%
Convalescent Serum	1627	1227	75.4%	273	16.8%	127	7.8%
Placental Extract	1341	959	71.5%	321	23.9%	61	4.6%

Figures for adult serum and convalescent serum collected from the literature

had actually been infected. This procedure served to increase the number of failures and modifications in comparison with the number of cases completely protected. However, it represented the most stringent test of the material. Under these circumstances, among 174 children given the material in order to protect them from the disease, 60.9 per cent were protected, 32.2 per cent had the disease in a modified form, and in 6.9 per cent the extract was without effect. Among 457 children similarly intimately exposed, who were given the extract later in the incubation period in order to secure modification of the disease, 45.5 per cent were completely protected, 46.8 per cent had the disease in a modified form and 7.7 per cent showed no amelioration in the severity of the illness. As regards dosage it would seem that placental extract is equal to or superior to fresh convalescent serum, inasmuch as the effective dosage has varied from two to six c.c. depending on the nitrogen content of the lot, whereas the dosage of convalescent serum is usually stated to be from four to eight c.c. and that of adult immune serum to be 15 to 20 c.c.

It was thought early in the investigations that the necessary dosage of various lots of extract might be determined by measuring the diphtheria antitoxin content. However, the anticipated parallelism between diphtheria antitoxin and the measles antibody was not found inasmuch as the distribution of the two antibodies was different. It was found to be possible to have a preparation effective against measles which contained no diphtheria antitoxin. Although at best it is a rough guide, the nitrogen content has remained the most reliable index of measles antibody content.

A study of the other factors influencing the effectiveness of placental extract in measles prophylaxis has been presented in some detail elsewhere.² Suffice it here to say that the material given by intramuscular injection in proper dosage is effective in the prevention and modification of measles, and that placental extract can be prepared on a large scale eliminating one of the obstacles which has hindered the wider use of serum in

measles prophylaxis In common with other types of passive immunization, the protection is of only a few weeks' duration, unless the disease occurs in modified form, in which case permanent immunity is generally believed to result However, accurate observations on the degree of modification that will still permit the development of permanent immunity have not been extensively made The studies of Debré indicate that the patient must have, although in mild form, definite symptoms of the disease⁶

REACTIONS

The intramuscular or subcutaneous injection of placental extract has been accompanied occasionally by moderately severe reactions The character of the reactions has seldom been that of specific sensitization Among the 1300 patients who have received the extract there were three cases of urticaria coming on within an hour and subsiding in 24 hours, apparently accelerated reactions of allergic type Two of these occurred in children with long allergic histories No cases of typical serum disease have followed the use of the extract, nor have instances of sensitization to subsequent injection of the extract been encountered, although numerous children have received several injections at intervals of weeks or months Reactions have consisted of local inflammation accompanied at times by fever Suppuration has not occurred, nor has a local reaction lasted longer than three to four days Febrile reactions characterized by temperatures as high as 103° F have lasted as long as 24 hours Among 1232 cases, mild local reactions occurred in 312, or 25.3 per cent, while more severe local reactions occurred in 49, or 4 per cent Febrile reactions occurred in 182, or 14.8 per cent Of these, 31, or 2.5 per cent, had temperatures above 101° The tissue protein may be in part responsible for reactions, inasmuch as injections of the tissue protein fractions, although prepared to contain less than half the nitrogen of the pseudoglobulin fractions have been followed by twice as many reactions

Several investigators have pointed out the marked toxicity of the press juice and of the saline extracts obtained from human placental tissue⁷ It was noted that the toxicity of such extracts was lost gradually, particularly if the extract remained in contact with normal serum Placental extracts prepared for immunologic use have likewise shown fewer reactions after aging than when used immediately after preparation In the lots recently prepared most of the tissue protein has been removed Reactions have been greatly reduced in frequency and severity but have not been entirely eliminated, indicating that tissue proteins are responsible for only a part of the difficulty Sex hormones are present in the extract in negligible amounts, apparently being almost completely removed in the process of preparation

IMMUNIZING EFFECT FOLLOWING ORAL ADMINISTRATION

Because of the short duration of immunity following the injection of the extract and the desirability of avoiding the unpleasantness of repeated injection, consideration has been given to trial of other methods of administration. Bovine lung tissue protein and human placental tissue extracts have been shown to be active in shortening the coagulation time of the blood following oral administration despite the susceptibility of these extracts to destruction by acids and alkalis and by intestinal ferments^{8,9}. The further consideration that the tissue protein (TG) was the largest protein aggregate which we have separated from the crude extract of the placenta, suggested that the antibodies might also be active following oral administration.

Studies of passive transfer tests and other allergic phenomena in both young and mature persons leave no doubt that at least minute amounts of protein may be absorbed from the gastrointestinal tract in antigenically active state by individuals of any age, without the intestines having been flooded with the protein and without the institution of measures to suppress intestinal functions¹⁰. Although the passage of minute amounts of unchanged proteins through the intestinal wall must be considered to occur with regularity, the passage of an antiserum in active form in sufficiently large amounts to render patients immune to disease cannot be deemed to be established.

Even if the proteins were absorbed unchanged, the duration of their presence in biologically active form in the blood stream following oral administration must be considered. In general, foreign proteins are thought to leave the blood stream within a few hours and to disappear from the urine in 24 hours. Obviously such a result would be unsatisfactory following administration of an antiserum.

The immunizing effect of placental extract by oral administration has been studied by observing the effect of ingestion of the extract on the Dick test of patients susceptible to scarlet fever, and the effect of the extract in the prevention and modification of measles in non-immune children intimately exposed to the disease. Before determinations of the immunizing effect were made, placental extract was ingested by members of the laboratory staff to be sure that the material did not cause digestive disturbances and that it was not unpleasant to take.

The immunizing effect of placental extract following oral administration could most readily be followed by testing for absorption of the scarlet fever antibody inasmuch as placental extract by intramuscular injection had already been demonstrated to render susceptible patients negative to the Dick test^{11,3}. Furthermore, not only could the reversal of the Dick reaction be readily determined, but the duration of such a reversal could be followed. In the series of tests placental extract in total amounts ranging from 9 to 20 c c varying somewhat with size and age of the child, was ad-

ministered in several doses of two to five c.c. each in ice-cold water on an empty stomach at least one hour before meals, according to the technic described by Mills for the absorption of the blood coagulant derived from lung tissue.¹ A Dick test performed 48 hours before the beginning of the administration of serum had been strongly positive in each person subjected to the test. The results of the test are shown in figure 2.

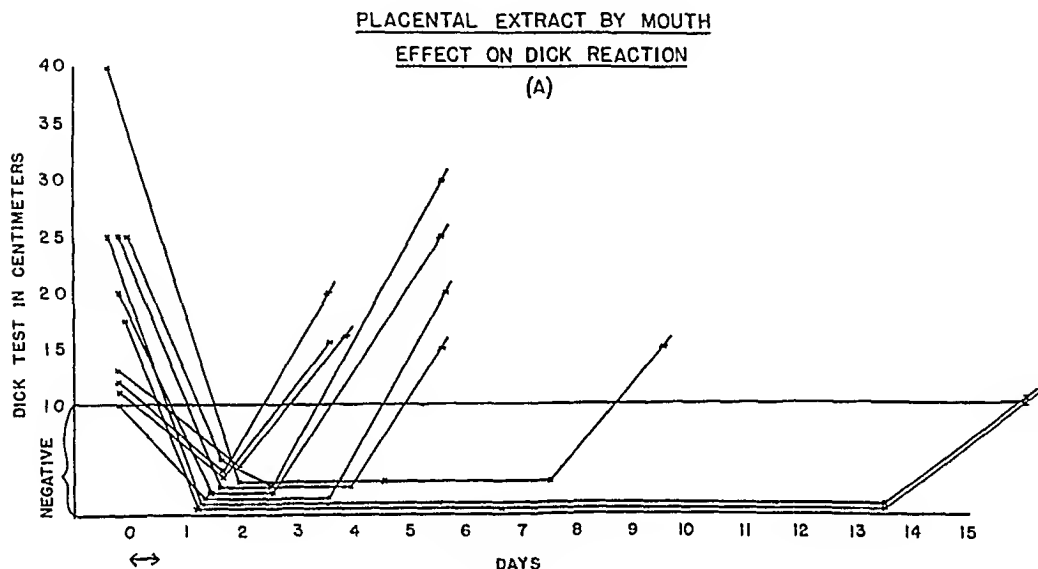


FIG 2 Placental extract given in three doses within a period of 12 hours, in ice water, on an empty stomach. The following morning Dick tests which were previously positive were entirely negative. The negative state, however, persisted for a comparatively short time.

It is to be noted that in these observations on children, in no instance was there a failure of the effect of the material, as in each instance a reversal of the Dick reaction was obtained. The duration of the effect, however, was quite variable. Presumably the short duration in several cases was due to the absorption of only a small part of the extract administered.

Various dosages and methods of administration have been employed in an effort to secure a more prolonged effect. One method has been the administration of the extract in an iced alkaline carbonated water. In figure 3 it will be seen that with this vehicle a prompt reversal of the Dick test was obtained in seven children who received the extract in this manner. Unfortunately not all of these patients could be followed until the Dick test had again become positive. However, in each patient the test remained negative seven days or longer. In one patient who could be followed the Dick test remained negative till the eighteenth day after administration of the extract.

In all, 22 children, ranging in age from 18 months to 10 years, have been studied and in each case a reversal of the Dick test has been obtained. Adults have required larger doses of extract than children and have devel-

oped a negative Dick test only after several days and in some instances not at all

PLACENTAL EXTRACT BY MOUTH
EFFECT ON DICK REACTION
(B)

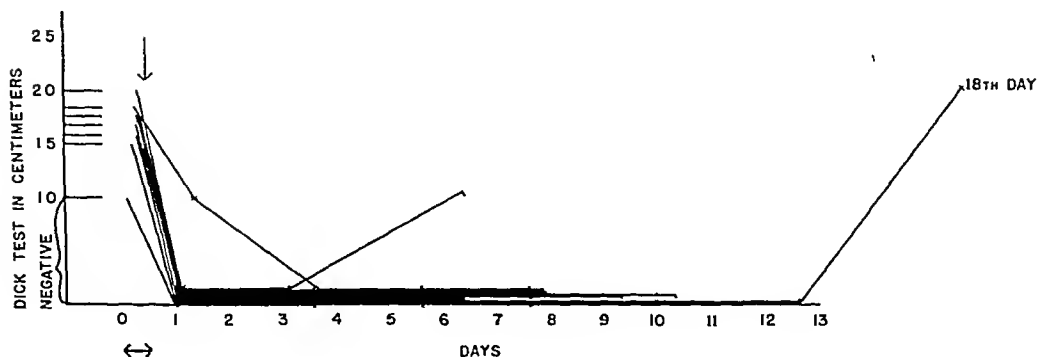


FIG 3 Placental extract given in three doses in iced alkaline carbonated water on an empty stomach. The following day Dick tests previously positive were negative and remained negative for a considerable period of time

The effectiveness of placental extract by oral administration in the prevention and modification of measles has been tested in over 100 patients. Eighty-four of these patients were non-immune children intimately exposed in their homes to other members of the family suffering from the disease. The results in these 84 patients where exposure was definitely known, are shown in table 3.

TABLE III
Prevention and Modification of Measles by Oral Administration of Placental Extract

		Protection	Modification	Failure
Given to Prevent	18	7	5	6
Given to Modify	66	15	32	19

If prevention was desired, the extract was given early in the incubation period. If modification was desired, the extract was given later in the incubation period of the disease. Although the group of patients in whom the extract was tested is not large enough to permit a statistical analysis of the results, there can be no doubt that placental extract by mouth has some effect in the prophylaxis of measles. However, the results are much less striking than those obtained by intramuscular injection of the material. The dosages used by mouth have been from two to three times those used for intramuscular injection. Further attempts to secure dependable results by the oral administration of the extract would appear justified.

No reaction has been observed in any patient who received placental extract by mouth although dosages up to 40 c c in 24 hours have been given. Material which caused moderately severe reactions when injected intramuscularly has been given by mouth without any untoward effect.

SUMMARY

Protein extracts composed of the globulins derived from the human placenta contain diphtheria and scarlet fever antitoxins, and antibodies which neutralize poliomyelitis virus and protect exposed, susceptible children against measles

The extracts can be prepared on a large scale and have been found useful in the prevention and modification of measles. Over 1300 children have received injections of the material. A small percentage of patients who have received injections of the extracts have had moderately severe local or general reactions.

Tests of the immunizing effect following oral administration of placental extract have been made.

Twenty-two children with positive Dick tests have been rendered Dick negative by the oral administration of the extract in cold water on an empty stomach. The duration of the negative stage has been variable but has been prolonged to as much as 18 days, if iced alkaline carbonated water was used as the vehicle. The reversal of the Dick test could not be obtained with any regularity in adults.

Tests of placental extract by oral administration in the prevention or modification of measles suggest that placental extract by mouth may be effective in this disease. Oral administration of the extract has not been accompanied by reactions.

BIBLIOGRAPHY

- 1 VON GROLR, F, and KASSOWITZ, K. Studien über die normale Diphtherieimmunität des Menschen, *Ztschr f Immunitätsforsch u exper Therap*, 1914, **xlii**, 404-450, *ibid*, 1914, **xliii**, 108-126.
- KUTTNER, A G, and RATNER, B. Importance of colostrum to new-born infant, *Am Jr Dis Child*, 1923, **xxv**, 413-434.
- PAUNZ, J, and CSOMA, E. Ensteht die Scharlachimmunität der Neugeborenen auf plazentarem Wege oder durch die Laktation?, *Jahrb f Kinderh*, 1930, **cxvii**, 181-186.
- AYCOCK, W L, and KRAMER, S D. Immunity to poliomyelitis in mothers and newborn is shown by neutralization test, *Jr Exper Med*, 1930, **lii**, 457-464.
- FINKELSTEIN, G S. Prevention of measles with puerperal serum, *Vrach delo*, 1931, **xiv**, 794-795, *abstr*, *Jr Am Med Assoc*, 1932, **xcviii**, 92.
- JORGE, R. Sur la sero-prevention de la rougeole au moyen du sang placentaire, *Bull Office internat d'hyg pub*, 1932, **xxiv**, 978-983.
- DE SOUZA, J S. L'immunisation contre la rougeole par le sang du placenta, *Arch de med d enf*, 1932, **xxv**, 633.
- 2 MCKHANN, C F, and CHU, F T. Antibodies in placental extracts, *Jr Infect Dis*, 1933, **lii**, 268-277.
- MCKHANN, C F, and CHU, F T. Use of placental extract in prevention and modification of measles, *Am Jr Dis Child*, 1933, **xlvi**, 475-479.
- 3 MCKHANN, C F, GREEN, A A, and COADY, H. Factors influencing the effectiveness of placental extract in the prevention and modification of measles, *Jr Pediat*, 1935 **vi**, 603.
- 4 ELEY, R C. *N E Jr Med* (In press)

- 5 MCKHANN, C F, and COADY, H Immunity in infants to infectious diseases, placental antibodies, *South Med Jr*, 1934, **xxvii**, 20-24
- 6 DEBRE R Sero-Abschwachung und Immunität gegen Masern, *Arch f Kinderh*, 1932, **xcv**, 169-175
- 7 SCHFINK, F Schutzeffekte normaler Sera gegen die Wirkung menschlichen Placentasaftes beim Kaninchen, *Zentralbl f Gynak*, 1909, **xxviii**, 1353-1356
- GAIFAMI, P Toxicity of aqueous placental extracts and the detoxifying action of blood serum, *Pathologica*, 1914, **i**, 415, also in *Zentralbl Biochem Biophys*, 1914, **xvii**, 74
- OBATA, I Detoxicating power of the body toward placental poisons, *Tokyo Igakukai Zasshi*, 1916, **xxii**, 19, also in *Japanese Med Lit*, 1917, **iv**, 2
- HAYASHI, T Antitoxic action of serum on placenta toxin, *Arch f Gynak*, 1923, **cxix**, 29-56
- 8 MILLS C A, and others Absorption from intestine and excretion through kidney of an unaltered complex protein substance, tissue fibrinogen, *Am Jr Physiol*, 1923, **lxiii**, 484-498
- 9 SAKURAI, K Studies on toxicity of human placenta upon rabbits and its accelerative influence upon coagulation of blood, and on its chemical nature, *Sei-I-Kwai Med Jr*, 1929, **xlvi**, 4-6
- 10 RATNER, B, and GRUEHL, H L Passage of native proteins through normal gastrointestinal wall, *Jr Clin Invest*, 1934, **xiii**, 517-532
- 11 ROSS, A S The effect of placental extract on the Dick test, *Jr Pediat*, 1935, **vi**, 546

FEVER THERAPY IN GONORRHEAL ARTHRITIS AND CHOREA¹

By TRUMAN G. SCHNABEL, M.D., F.A.C.P., and FERDINAND FETTER, M.D., *Philadelphia, Pennsylvania*

GONORRHEAL ARTHRITIS

FOR the past forty years there have been occasional reports of cure of gonorrheal infections during a febrile illness. In 1893 Bogdan and Baithelémy¹ told of a gonorrheal discharge which disappeared during an attack of pneumonia and recurred after the fever subsided. They also noted two cases in which the development of typhoid fever caused a gonorrheal discharge to disappear. Culver² noted the cure of a urethral infection of Neisserian origin after four days of malaria. However, it was not until the work of Carpenter, Boak, Mucci and Warren,³ who determined the thermal death time of the gonococcus, that the use of fever in treating this type of infection was put on a scientific basis. These investigators, working with 15 strains of the organism, found that 99 per cent of them were destroyed at a temperature of 41° C (105.8° F) in four to five hours. From 11 to 23 hours longer at this temperature were required to kill the remaining 1 per cent. At a slightly higher temperature, between 41.5° C (106.7° F) and 42° C (107.6° F), 99 per cent of the gonococci were killed in two hours while the remaining 1 per cent required five to twenty hours longer. These workers thus showed conclusively that the gonococcus could be killed by a temperature which the human body could tolerate. It remained only to perfect a safe and accurate method for inducing temperature of this height.

Fever produced by various methods has been used clinically in treating arthritis of gonococcal origin since 1917, and in all reported cases with better results than with any other form of treatment. Culver² used intravenous injections of killed gonococci, meningococci, or colon bacilli to produce the fever and reported marked improvement in 22 of 24 patients so treated. He did not, however, attribute this improvement to the fever per se. Dumitresco and Petrea,⁴ using antichancroidal vaccine to elevate the temperature, reported excellent results in five cases of gonorrheal arthritis. More recently, various physical methods of inducing fever, which are more accurate and can be better controlled, have been used. Bishop, Horton and Warren,⁵ using high frequency currents to produce the fever, stated that of all the arthritic patients treated by them, those with gonorrheal arthritis were the most improved. Atsatt and Patterson,⁶ employing electroprexia,

* Read before the Fifth Annual Fever Conference at Dayton, Ohio, May 2, 1935, and before a Clinical Session of the Nineteenth Annual Meeting of the American College of Physicians, held at the Philadelphia General Hospital, May 3, 1935.

From the Department of Fever Therapy, Philadelphia General Hospital, Philadelphia, Pennsylvania.

reported recovery in 7 out of 8 cases of acute gonococcal arthritis Desjardins, Stuhler and Popp,⁷ using the Kettering hypertherm, which I shall describe presently, have reported good results with fever therapy in 29 cases of gonorrhea, in 10 of which gonorrheal arthritis was a complicating factor

The Kettering hypertherm, which we have used also, has been developed by Dr Walter M Simpson of the Miami Valley Hospital at Dayton Ohio, Mr C F Kettering, Director of Division of Research of General Motors Corporation, and Mr Edwin C Sittler, engineer in the same organization In this apparatus the patient lies free in an air conditioned cabinet, surrounded by a moving current of heated and humidified air, by means of which the temperature is raised No electrodes are in contact with the patient and no high frequency currents used The patient's temperature and pulse are taken every 15 minutes or oftener The temperature reaches the desired level in from 60 to 90 minutes More detailed descriptions of this method and technic have already been given.^{7, 8, 9}

The contraindications to fever therapy must be heeded, such as advanced age, renal and cardiac disease (particularly the hypertensive and arteriosclerotic types) and, in general, pulmonary tuberculosis It must likewise be emphasized that treatments should be given only by trained nurse technicians, one to a patient, who keep continual watch over the patient, and that the work must be under the constant supervision of a physician who has been especially trained in fever therapy It must be remembered that any fever treatment is a serious and a difficult procedure and that a patient should never be subjected to it without thorough preliminary study

Cases of Gonorrheal Arthritis Treated The technic of the treatment of these patients is as follows the temperature is raised to 106° F (rectal) and maintained between this level and 107° F (rectal) for 5 hours This constitutes one treatment The treatments are given at weekly intervals, the number required varies, but is usually from two to five

At the Philadelphia General Hospital, we have treated 18 patients with gonorrheal arthritis by fever induced in the Kettering hypertherm In nine of these cases, the arthritic process was acute (of less than six weeks' duration), in nine it was chronic (of more than six weeks' duration) Diagnosis of the gonorrheal etiology of the arthritis was made on the basis of a history of a purulent urethral or vaginal discharge which had been diagnosed gonorrheal in origin, the finding of the gonococcus in urethral, prostatic or cervical smears or the presence of a positive gonococcal complement fixation reaction in the blood, or a combination of these findings

Acute Gonorrheal Arthritis In this group of nine patients, the average duration of the arthritic symptoms before treatment was three and one-half weeks The earliest case treated was of two weeks' duration, the oldest case was of five weeks' duration The number of treatments given each patient varied from two to six, the average number of hours of treatment over 106° F was 14.5 hours per patient corresponding to an average of

three treatments per patient. In two of these patients the gonococcal complement fixation reaction in the blood was positive before treatment. One of these reactions became negative after completion of the series. One remained positive although this was in one of the patients clinically cured. Positive urethral or cervical smears, when present, became negative after treatment, and any discharge, if present, likewise stopped. The improvement in the involved joints was striking in all cases, and in some almost miraculous. Invariably there was marked diminution in swelling and redness of the involved joint after the first treatment, and marked decrease in pain associated with definite increase in movement. The improvement was most rapid in the most recently involved joints. The temperature of the patient was invariably lower after the first treatment than it had been before. One patient who had had continuous fever going as high as 102.5° F. before treatment had no elevation of temperature after the first fever session.

Six of the nine patients were cured by the fever treatments, with no other form of therapy. Two of the remaining three showed about 80 per cent improvement after fever therapy alone, but needed baking and massage of the affected joint to get complete return of movement. In only one case was the result relatively poor. This patient still has a partial ankylosis of the left elbow, although she is able to perform practically all necessary movements with this arm and there is no active infection left in the joint. We felt that her end-result was not as good as it should have been only because she did not receive enough treatments. Because of extreme lack of cooperation on her part and a peculiar difficulty in raising her temperature we were able to give her a total of only nine hours and 50 minutes over 106° F.

These results are summarized in table 1.

Chronic Gonorrheal Arthritis. In this group of nine patients the average duration of the arthritic symptoms before treatment was seven and one-half months. The earliest case treated was of three months' duration, the oldest of 18 months'. The number of treatments varied from one to six. One of the patients received only one treatment because he did not return for subsequent sessions as he had been instructed to do. However the reason for this, as we learned on follow-up examination, was that he had been entirely symptom-free after the first treatment. The average number of hours of fever over 106° F. was 18 per patient, corresponding to an average of approximately three and one-half treatments per patient. Three of the nine patients had positive gonococcal complement fixation reactions in the blood before treatment was started. All of these reactions became negative after the treatments were completed. Positive cervical and prostatic smears, when present, also became negative, and any chronic discharge, if present, stopped. The joint symptoms of all of these patients improved, although usually not as rapidly as they did in the acute cases.

Of the nine patients five were cured and have remained so since completing their treatments (for periods of from three to six months), except that one of these patients developed a fresh case of gonorrhea and con-

sequent new joint pains for which we can feel no responsibility. Three of the nine patients showed marked improvement. They obtained complete eradication of the infected process in the involved joints with relief from pain, and had a partial return of movement. Two of these three patients had previously been bed-ridden with continuous fevers for periods of three and one-half and three months respectively before treatment. After completing the fever sessions, and with local physiotherapy (baking and massage) they have been able to return to doing light housework. Only one of the nine patients has shown merely moderate improvement after treatment. He has marked increase in movements of the involved joints, but still has occasional pains.

These results are summarized below.

TABLE I
Cases of Gonorrheal Arthritis Treated with Fever Therapy

	Number of Patients	Average Duration of Symptoms before Treatment	Average Number Hours Treatment over 106 F	Results		
				Cure	Marked Improvement	Moderate Improvement
Acute	9	3½ weeks	14½ hours	6	2	1
Chronic	9	7½ months	18 hours	5	3	1

CHOREA

Fever therapy for its own sake was first used in the treatment of Sydenham's chorea by Mas de Ayala¹⁰ in 1930. This investigator used the *Treponema hispanicum* to produce relapsing fever in a boy with chorea of two years' duration. After four febrile attacks improvement began and continued until the boy was cured. Prior to this work improvement in patients with chorea had been noted by von Kern¹¹ as a result of intramuscular injections of milk, but the improvement was not attributed to the resulting fever. Horton¹² likewise observed improvement in two patients with chorea after intravenous injections of a pure protein prepared from ox-blood fibrin. He did not mention whether there was a febrile reaction, but undoubtedly there was. In 1928 Small¹³ reported improvement in 24 of 25 patients with chorea treated with his *Streptococcus cardioarthritidis* antiserum. However, he considered that the improvement was due to the specific serum and not to a non-specific protein reaction with associated fever. In 1913 Pilcher and Gerstenberger¹⁴ noted that the patients with chorea who were improved after treatment with phenyl-ethyl-hydantoin (nirvanol) were those who reacted to the drug by developing a rash and a fever, while those not so reacting were not benefited.

Sutton¹⁵ was the first to use fever therapy in a large number of patients with chorea. This worker had noted improvement in a patient who had re-

ceived phenobarbital to the point of toxicity and who had developed a rash and a fever. Believing that the fever was the beneficial agent in this case, and in the reported cases of improvement with phenyl-ethyl-hydantoin, she decided to try typhoid-paratyphoid vaccine intravenously to produce fever. Her results, reported in this and in a later paper,¹⁶ were very gratifying. In the latter she compared the results of 150 cases of chorea treated without fever prior to 1930 with 150 cases treated with fever after 1930. There was a striking reduction in the duration of the disease in all fever treated cases compared with those not so treated.

Many reports of the use of typhoid-paratyphoid vaccine to produce fever in patients with chorea have appeared since Sutton's work. All investigators have found that the course of the disease is noticeably shortened by this method of treatment. Another type of fever producing agent used in treating chorea was "Soufrogel," a sulphur gelatine preparation used by de Castro-Freire¹⁷ intramuscularly. The resulting elevation of temperature to 38.5° to 40° C. was effective in reducing the duration of the disease in 11 cases so treated.

In view of these facts it was logical that physical means of inducing fever should be tried in treating these patients. While no more effective than fever induced by typhoid-paratyphoid vaccine, this method is, we feel, more accurate and the fever more easily controlled.

In our first cases we used temperatures of 103° to 104° F. for three hours and repeated the treatments at weekly intervals. Subsequently we found that the patients improved more rapidly after temperatures of 105° to 106° F. and with treatments given twice a week. Our present technic is, therefore, to give three hour sessions at 105° to 106° F. twice weekly. As many treatments as are needed are given, usually from three to five suffice. In our experience the presence of a coexisting rheumatic cardiac lesion has not been a contraindication to the treatment. Several of our patients had rheumatic mitral valve lesions and behaved as well under treatment as did those whose hearts were apparently normal.

Cases of Chorea Treated. We have completed treatments on 11 children affected with Sydenham's chorea. Of these, three had severe choreiform movements (one was so active as to require constant restraint), six had moderately severe chorea, and in the remaining two the condition was relatively mild. The age of the patients varied from 4 to 15 years. The duration of the disease before treatment was given varied from three and one-half weeks to two years (this last was one of the mild cases). In seven of the eleven patients, however, the duration of the symptoms was less than six weeks. The average number of treatments given was four, each treatment consisting of three hours of elevated temperature. In six of the eleven children there was an associated mitral valvulitis. The other five had no evidence of heart disease.

In most cases there was a striking diminution of the choreiform movements after the first treatment. In general the degree of improvement was

proportional to the severity of the process, those with the most marked movements showing the most rapid improvement. We also observed that the children with generalized movements improved more rapidly than did those in whom the movements were localized. Of the 11 cases, nine were cured after their treatments and so far (from one to six and one-half months afterwards) have not shown any recurrence. The other two did not show complete cessation of their symptoms. One child still has slight incoordination of the right hand in performing voluntary movements but he is able to be back at school and to keep up with his class. The other child has continued to have slight movements of both arms when excited. It seems significant that both of these children were among our earlier subjects on whom we used the lower temperatures. We believe that higher temperatures would have cured them, but they were so much improved by the lower temperatures that further treatment seemed a counsel of perfection.

In all cases, the rapid improvement after the first or second treatment, with no other form of therapy, showed clearly that the fever was the effective therapeutic agent. The older children even realized this themselves and after the first one or two treatments were anxious for more in spite of the discomfort attendant upon these sessions. In those cases in which there had been previous attacks of chorea the family physician or the parents said the improvement was much more rapid with fever therapy than without.

These results are summarized in the following tabulation.

TABLE II
Cases of Chorea Treated with Fever Therapy

Number of Cases	Age Range	Duration of Symptoms before Treatment	Average Number of Treatments	Results	
				Cure	Marked Improvement
11	4-15	3½ wks to 2 yrs (in 7 cases less than 6 weeks)	4	9	2

One case of chorea treated by us has not been included in the series above because of a fatality following the first partial fever session. This was a boy of 12 years with moderately severe chorea of three weeks' duration, and with no history of any previous rheumatic infection (rheumatism sore throats or previous attack of chorea). His heart was normal on physical examination and his electrocardiogram was normal. After being in the cabinet for only one and one-half hours, he suddenly went into collapse with a fall of blood pressure to zero, marked cyanosis, and a cardiac rate of over 180. He was immediately removed from the cabinet and given treatment for shock. His temperature rose to 108° F (rectal) but it responded to sponges and other fever reducing measures. His condition improved gradually but steadily for nine hours after being removed from the cabinet. His

temperature dropped to 101° F (rectal), his cyanosis diminished markedly and he was entirely conscious and responded normally. His cardiac rate remained at 160 but was regular. His clinical condition at this time seemed quite satisfactory. Subsequently, however, his temperature and cardiac rate rose again and the cyanosis returned. This time efforts at stimulation and reduction of the temperature were without effect. He died 17 hours after his initial collapse.

At autopsy the chief gross changes were in the brain. These consisted of intense edema and venous congestion. Grossly, the heart was entirely normal. The adrenals showed mild parenchymal degeneration and the thymus slight hyperplasia. There was acute passive congestion of the lungs, spleen, liver, kidneys and the gastrointestinal tract. Thus it seems apparent that death was due to a cerebral disturbance and particularly a disturbance in the heat regulating mechanism.

It is clear that this death was a direct result of the fever treatment, but it should be stressed that this boy was treated under exactly the same conditions as the many patients we have successfully treated and that he seemed in every way an excellent subject. Such a death is perhaps comparable to the unforeseen deaths under anesthesia and should be viewed in the same light. Only time and a compilation of facts will tell whether such accidents are to be so frequent as to counterbalance the favorable results of fever therapy or whether, as in the case of anesthesia, they will be but an unfortunate but relatively small item in a desirable and beneficial whole. We hope and believe the latter will be the case.

SUMMARY AND CONCLUSIONS

Fever induced by circulating humidified hot air in the Kettering hypertherm was used in treating 18 cases of gonorrheal arthritis, nine acute and nine chronic, and 12 cases of Sydenham's chorea.

Of the nine patients with acute gonorrheal arthritis, six were cured, two were markedly improved, and one was moderately improved. Of the nine with chronic gonorrheal arthritis five were cured, three markedly improved, and one moderately improved.

Of the 12 patients with chorea, nine were cured and two markedly improved. One died as a result of a disturbance of his heat regulating mechanism.

With the exception of this unpredictable accident, no case of either of these diseases has failed to respond favorably to this form of treatment. We believe that fever therapy offers the best chance of cure for both gonorrheal arthritis and chorea.

BIBLIOGRAPHY

1. BOGDAN, M, and BARTHELEMY, M. Disparition d'un écoulement blennorrhagique pendant le cours d'une pneumonie, retour de l'écoulement après la guérison, *Ann de dermat et syph*, 1893, iv, 253-254.
2. CULVER, H. The treatment of gonorrheal infections by intravenous injections of killed gonococci, meningococci, and colon bacilli, *Jr Am Med Assoc*, 1917, lxxviii, 362-366.

- 3 CARPENTER, C M, BOAK, R A, MUCCI, L A, and WARREN, S L Studies on physiologic effects of fever temperatures, Jr Lab and Clin Med, 1933, xviii, 981-990
- 4 DUMITRESCU, T, and PETREA, C La pyrethotherapie des arthrites gonococciques, Bull et mem Soc med d hop de Paris, 1933, xlix, 1480-1483
- 5 BISHOP, F W, HORTON, C B, and WARREN, S L Clinical study of artificial hyperthermia induced by high frequency currents, Am Jr Med Sci, 1932, clxxiv, 515-533
- 6 ATSATT, R F, and PATTERSON, L E Use of electropyrexia in gonorrheal arthritis Physiol Rev, 1933, xiii, 143-146
- 7 DESJARDINS, A U STUHLER, L G, and POPP, W C Fever therapy for gonococcic infections, Jr Am Med Assoc, 1935, civ, 873-878
- 8 KRUSEN, F H Recently developed method of artificial fever production by physical means, Med Rec, 1934, cxl, 248-250
- 9 SIMPSON, W M Artificial fever therapy, report of researches at Miami Valley Hospital, Proc Staff Meet Mayo Clinic, 1934, ix, 567-571
- 10 MAS DE AYALA, L Piretoterapia Aplicacion del *Treponema hispanicum* para el tratamiento del Parkinsonismo encefalitica y de la corea de Sydenham, Sem med, 1930 xxxvii, 857-867
- 11 VON KERN, T Die Behandlung der Chorea minor mit Milchinjektionen, Wien klin Wchnschr, 1923, xxxvi, 164
- 12 HORTON, E G Treatment of chorea by intravenous injections of pure protein, Ohio State Med Jr, 1922, xviii, 751-753
- 13 SMALL, J C Rheumatic fever observations bearing on specificity of *Streptococcus cardioarthritidis* in rheumatic fever and Sydenham's chorea, Am Jr Med Sci, 1928 clxxv, 638-649
- 14 PILCHER, J D, and GERSTENBERGER, H J Treatment of chorea with phenyl-ethylhydantoin, Am Jr Dis Child, 1930, xl, 1239-1249
- 15 SUTTON, L P Treatment of chorea by induction of fever, Jr Am Med Assoc, 1931, xcvi, 299-301
- 16 SUTTON, L P, and DODGE, K G Treatment of chorea by induced fever, Jr Pediat, 1933, iii, 813-826
- 17 DE CASTRO-FREIRE, L La pyrethotherapie dans la choree, Arch de med d enf, 1932, xxxv, 527-536

DERMATOMYOSITIS, REPORT OF A CASE WITH A REVIEW OF THE LITERATURE¹

By ISRAEL H. MARCUS, M.D. and JOSEPH WEINSTEIN, M.D.,

Brooklyn, New York

DERMATOMYOSITIS is a disease still frequently unrecognized. Because of this and the relative rarity of the condition, as well as the profound and extensive changes found postmortem in our patient, we have deemed the following case and a review of the literature as worthy of publication.

CASE REPORT

J. K. was admitted to the Jewish Hospital on May 18, 1931, complaining of generalized weakness and difficulty in swallowing and speaking. He was of the Hebrew race, born in the United States, 44 years of age, and a paper cutter by trade.

Family History—Negative except for the fact that two of his maternal uncles and three of his sisters had all died of carcinoma of the stomach.

Past History—The patient had had scarlet fever in childhood without any complications, pneumonia at 17, influenzal bronchopneumonia at 31, bilateral keratitis according to his belief, since birth but inactive for the last 15 years, and frequent sore throats for many years. Two months before admission (i.e., one month after the onset of the present illness) he suffered a generalized urticarial rash following the administration of tetanus antitoxin for an injury to a finger.

He had always worked hard. He used alcohol, tobacco, tea and coffee in moderation. He had been married 22 years and had seven healthy children. His wife had one miscarriage—in her fourth pregnancy.

Present Illness—Three months before admission to the hospital the patient noticed soreness and weakness in both arms and forearms, occurring with activity. Associated with this there was a gradually increasing limitation of motion of the elbows and shoulders. Two months after the onset, the soreness and weakness were felt in the lower extremities, involving later the muscles of the lower back and pelvis also.

Two months before admission he first experienced an inconstant, but progressive, dysphagia, at first noted only with the taking of solids but later with liquids as well. The food seemed to him to get stuck in the suprasternal region, and there was frequent regurgitation through the nose.

For the last six or eight weeks he had been hoarse, and for the last 10 days there had been a rapid fatiguing of the organs of speech, affecting markedly his pronunciation.

He had had a slight cough for about six weeks and in the last two weeks a slight dyspnea.

Three days previously he had first noticed a swelling of his face and arms. He had never observed any muscular twitchings or atrophies. There was no history of double vision. There was no apparent loss of weight.

Physical Examination on Admission—The temperature was 100.2° F, pulse 90, respirations 18, per minute.

The patient was a hyposensitive individual, appearing comfortable, fairly well nourished, cooperative and intelligent. His hair was gray, with scattered areas of

¹ Received for publication January 16, 1935.

From the Meyer A. Rabinowitz Medical Service of the Jewish Hospital of Brooklyn.

alopecia of the scalp. There was an erythema and dry scaliness of the scalp, nose, nasolabial folds, and ears. The lower eyelids were edematous, and there was a puffiness and irregular erythema of the cheeks. The face had a peculiar mask-like appearance, but a display of emotion could be elicited. The pupils were equal in size, slightly irregular, and reacted well to light and accommodation. The fundi were normal. There was a keratitis of both eyes, with pannus formation and scarring of the conjunctiva of the lids. The ophthalmologist considered the condition an old trachoma with corneal involvement. The few remaining teeth were carious. There was a postnasal drip. The uvula drooped abnormally, but the pharyngeal reflex was present. The thyroid was palpable, but not enlarged. There was a generalized acne of the chest anteriorly and posteriorly. Lung examination revealed harsh breathing at the right apex, an occasional moist rale at the right base posteriorly, and a suppression of the breath sounds and fine crepitant rales at the left base posteriorly. The heart was normal in size, and regular in rate. There was a roughening of the first sound at the apex with a suggestion of a presystolic murmur. The second pulmonic sound was accentuated. Blood pressure was usually about 125 mm Hg systolic and 75 mm diastolic. There was no abdominal tenderness or spasticity, and no viscera or masses were palpable. The rectal sphincter was somewhat relaxed. The prostate and genitalia were normal.

There was a slight swelling of the upper part of the arms, more marked on the right, and a diminution in the muscular power of the upper extremities, more marked on the left side. There was a flexion deformity, with inability to flex both elbows beyond 15 or 20 degrees. Forced flexion caused considerable pain. There was muscle tenderness on deep palpation. The muscles of the lower extremities appeared smaller than normal. The knees could not be flexed beyond about 15 degrees. There was weakness of the muscles of the pelvic girdle, and when the patient bent forward it required marked effort to return to the erect posture.

Neurological examination showed no cranial nerve involvement. The biceps and triceps reflexes were normal. The deep reflexes were present but became depressed after repeated testing. The abdominal reflexes were normal. There were no extra-ocular palsies. Hoffmann's sign was not present. There was a left-sided equivocal Babinski and at times a bilateral Oppenheim. There was no ankle clonus. Coordination was good. There was no impairment of the cutaneous sensations. Idiomyotonic contractility was marked over the upper extremities and chest. Marked dermatographia was present. There was an atrophy of the thenar and hypothenar eminences and of the interossei in both hands.

Biopsy of a section of the left biceps showed on microscopic examination the following. The muscle fibers are swollen. The protoplasm assumes a fibrillar appearance, with a disappearance of the transverse striations. In some the protoplasm is homogeneous and presents a hyaline appearance. Various stages of degeneration of the muscle cells are noted, from the cloudy swelling, above described, to complete degeneration and loss of identity. There is a moderate increase in the connective tissue, which is quite dense. In the areolar tissue the large blood vessels appear normal. The arterioles, however, in many cases show rather extensive perivascular round cell infiltration. No thrombosis or occlusion of vessels is noted.

Spinal tap on May 28 showed red blood cells in the fluid, negative Wassermann and Kahn reactions, and no reduction of colloidal gold. Culture of the fluid gave no growth.

Röntgen-ray of the chest on May 20, revealed a bilateral hilum infiltration and an exaggeration of the pulmonary markings, but no evidence of localized disease. There was no radiographic evidence of a thoracic thyroid. The cardiac shadow was within normal limits of size, shape and position.

Fluoroscopic and roentgen-ray examination of the esophagus on May 26 revealed a slight delay in the passage of the opaque paste at the level of the upper end

of the sternum, which delay persisted for a few minutes, after which the opaque column passed readily through the esophagus. These findings, the roentgenologist believed, suggested the presence of spasm or localized muscular weakness.

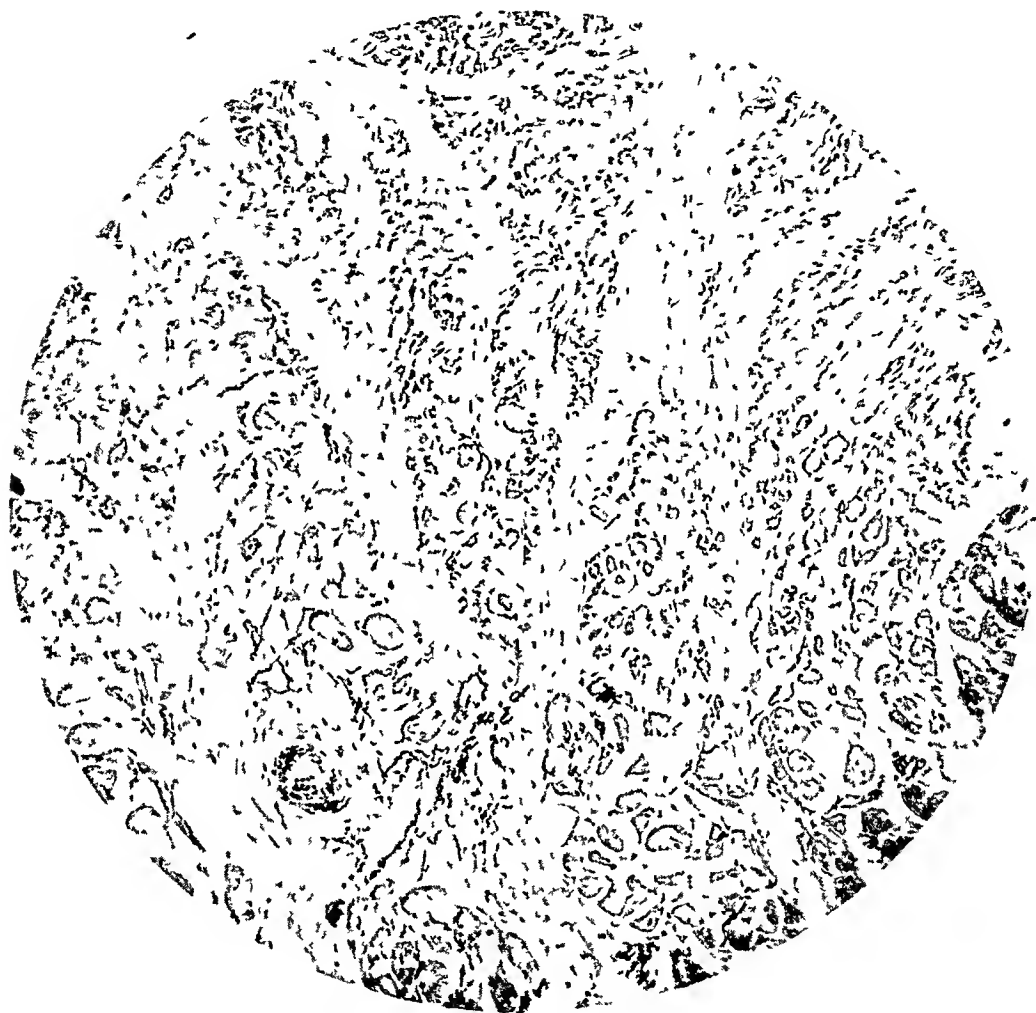


FIG. 1. Section of muscle.

Electrocardiogram on May 21 showed a ventricular rate of 107. R was slurred in all leads, the T-wave in Lead II was low, and in Lead III inverted. Q_3 was deep. These findings suggested the existence of myocardial damage.

Glucose tolerance test. Blood sugar, fasting, at 8 a.m. was 175 mg per 100 c.c., at 9 a.m. (one hour after ingestion of 100 grams of glucose) 205 mg per 100 c.c., at 10 a.m. 295 mg per 100 c.c., and at 11 a.m. 206 mg per 100 c.c. The urine at all these hours showed no sugar. These results were interpreted as evidence of a disturbed sugar metabolism, diabetic-like in nature, with a high renal threshold.

Blood chemistry tests on a fasting stomach were: Sugar 150 mg per 100 c.c., creatinine 1.5 mg per 100 c.c., urea nitrogen 15.6 mg per 100 c.c., and uric acid 3.7 mg per 100 c.c.

Blood Wassermann and Kahn tests, repeated on several occasions, were constantly negative

Urines, tested a number of times, showed a specific gravity varying between 1 018 and 1 030, were always acid, and never showed any albumin or sugar or pathological microscopic sediment



FIG 2 Section of skin

Blood count on admission was Red blood cells 3,800,000 with 75 per cent hemoglobin White blood cells 7,000 with 64 per cent polymorphonuclears (of which 8 per cent were band forms), 32 per cent lymphocytes, 4 per cent large mononuclears and transitional cells, and no eosinophiles

Blood sedimentation time was 40 minutes for 18 mm

Basal metabolic rate was plus 3 per cent

Roentgen-ray of the chest on June 2 suggested an infiltration of the lungs on the left side Sputum examination showed no tubercle bacilli, but revealed Gram negative and positive bacilli with spirilla and fusiform bacilli and micrococci catarrhals Culture of the sputum showed *Staphylococcus aureus*

On June 5, three days before death, pitting edema of the lower extremities was noted, but there was no sacral edema or any edema over the rest of the trunk. The same day the patient experienced very much more difficulty in swallowing than previously.

The temperature ranged throughout between 100° and 101° with an occasional elevation to 103°. On the day before death it rose to 104°, and the respirations rose that day to 50 per minute. Moist râles were heard over the entire chest. Mucus had to be suctioned from the throat. The pulse became imperceptible and the heart sounds very weak. The patient grew worse, and died on June 8.

Treatment included the following: Pilocarpine gr 1/20 thrice daily, ephedrine sulphate gr 3/8 thrice daily, at first, and later increased to gr 1 1/2 thrice daily, finally quinine urea hydrochloride gr 7 1/2 was used intravenously each day, and calcium lactate gr 20 thrice daily was also given. Nothing seemed to have any beneficial effect.

AUTOPSY FINDINGS

The body is that of a markedly undernourished white male. The cheeks and eyeballs are sunken. The skin is dry and loose over the entire body. The subcutaneous tissue is reduced to a minimum. The muscles are extremely thin and edematous, and in areas present a gray hue.

Microscopic examination of pieces of *skin and muscle* taken from the surface of the chest and abdominal wall and from the muscle of the diaphragm and psoas muscle shows a marked atrophy of the cutis and a fibrosis of the subcutis. The fat normally present in the subcutis has completely disappeared, and the fat tissue is replaced by fibrous material. The muscle shows the following: Many of the cells have lost their cross striations, some are hyalinized, some are undergoing fibrillar changes, and many show complete disintegration of the cytoplasm. Vacuolization is present, and numerous plasma cells have infiltrated the muscle. The nuclei of the muscle cells are either thinned out and tortuous, or clumped together, or broken up. Marked edema separates individual cells. There is a perivascular round cell infiltration, which is nodular in distribution. Some of the vessels show an endothelial hyperplasia and contain fibrin thrombi and enmeshed leukocytes. Clumps of short bacilli and cocci are present in some of the muscle sections.

Macroscopically the *thyroid* appears normal, but on microscopic examination purulent thrombi are found occluding large veins, and one of these thrombosed veins shows a suppurative process in the intimal coat.

Larynx The epiglottis is extremely edematous, as are also the aryepiglottidian folds. The vocal cords are pale, and also markedly edematous.

The mucosa of the *trachea* is congested and edematous.

The *bronchi* are congested and the smaller divisions contain a marked amount of pus and lead into patches of pulmonary consolidation.

There are some dense adhesions binding the *lungs* in places to the chest wall. The rest of the lungs is covered by a fibrinous exudate. The lungs show an extensive purulent bronchiolitis and suppurative pneumonitis.

The *peribronchial lymph nodes* are enlarged, soft, and red-blue in color.

The *myocardium* is edematous and shows on microscopic examination a moderate amount of atrophy. There are no changes in the heart muscle similar to those found in the skeletal muscles.

The *aorta* presents grossly a moderate amount of atherosclerosis.

The *liver* shows a parenchymatous hepatitis with fat infiltration.

In the upper portion of the *esophagus* are several superficial ulcerations, the bases of which microscopically show a large number of hyperplastic glands and chronic inflammatory tissue. The germinal centers of the mucosa are markedly hyperplastic. The muscle of the wall of the esophagus shows degenerative changes consisting of

granular disintegration There is a marked edema involving all layers of the organ

The *stomach* is normal except for a congestion of the mucosa

The external muscular coat of the *large intestine* contains a markedly increased number of nerve ganglia, the individual cells of which ganglia show neurotrophic changes The mucosa is ulcerated in one area, the base of the ulceration being also the site of a chronic inflammatory process Numerous thick coccoid bacilli are seen

The *kidneys* and *spleen* are congested and show also cloudy swelling

There is a parenchymatous degeneration of the *pancreas* and *adrenals*

The cells of the *bone marrow* are hyperplastic and numerous cocci are seen

The *brain* is extremely edematous

The *femoral nerve* is undergoing changes consisting of vacuolization of the cell cytoplasm The process, however, is mild in character

HISTORICAL

The earliest recorded case of dermatomyositis is one that was described by Wagner¹¹¹ in 1863 under the title of "A Rare Muscular Disease" Twelve years later, in 1875 Potam⁸¹ recorded another case, calling it "an atypical case of chronic glanders" In 1887 the condition was carefully described by three authors independently of one another—Wagner,¹¹² Hepp,⁴¹ and Unverricht^{106, 107, 108} Hepp called the disease "Pseudotrachinosis" Unverricht was the first to call it "dermatomyositis," an excellent name, for in this disease there exists an inflammation of the muscles (a polymyositis) associated with skin manifestations, such as edema and dermatitis In 1888 Senator^{93, 94, 95} described a type of polymyositis with involvement of the peripheral nerves, and called this condition "Neuromyositis" Oppenheim in 1899⁷⁹ and 1903⁸⁰ called attention to the fact that in this disease not only were the muscles and skin affected but that the mucous membranes of the mouth, throat, and larynx might also be involved, and for such cases he coined the term "Dermato-muco-myositis" Oppenheim⁸² in his textbook of 1923 described this disease with great thoroughness and clarity, and although in the preparation of this present article the authors have culled freely from the publications of all who have previously written on the subject, to Oppenheim beyond all others we are obligated In view of the possible involvement, as in the case we have reported, of skin, mucous membranes, muscles and nerves, the best name given to the condition, we believe, has been "Dermato-muco-neuro-myositis" Probably in the group of cases of dermatomyositis we should include the cases collected by Lorenz⁶⁸ in 1898 under the title "Polymyositis hemorrhagica," in which there is an inflammatory sanguineous infiltration into and between the affected muscles, or in which there has been an ecchymotic discoloration of the skin In these cases purpura and hemorrhages may occur from the mucous membranes or into the myocardium¹²⁰

OCCURRENCE

Dermatomyositis occurs in both males and females, but is probably somewhat more frequent in the former⁸² Although usually occurring in

adult life, it may be seen at any age. Lehmkuhl,⁶² reviewing the literature between 1895 and 1928, found 16 cases in children, the two youngest being three years old. Demel¹⁹ reported a case of "Sclerema of the Newborn in the Form of Polymyositis." It commenced on the second day of life, and the child died when nine days old. He believes that the multiple inflammatory alterations in the infant's skin and muscles were the same as those found in adults in dermatomyositis.

ETIOLOGY

Although much has been written on the etiology of this disease, and although many interesting observations have been reported in connection with the study of the cause of the disease, at the present time we have no definite knowledge as to its etiology.

Most of the authors who have attempted to determine its causation have thought it to be due to some infectious agent. A number of facts have suggested this infectious etiology: the fact that the disease is more common in winter than in summer,³¹ the existence of an enlarged spleen in the acute stage in many of the cases, the albuminuria, the rash that is so frequently present,⁸³ and the occurrence of a few instances in epidemics.^{65, 97} In some cases bacteria have been found in the blood stream,^{3, 52, 74, 78} in the muscles,^{5, 37, 69, 120} and subcutaneous tissues.^{30, 78} But the instances in which organisms could be thus discovered are but relatively few compared to the total number of cases that have been reported. If the disease were due to a microorganism one would expect it to be found much more often than it has been demonstrated. Various bacteria have been accused as the cause of the disease—"micrococcus polymyositicus,"^{28, 73} streptococci,^{24, 30, 60, 78, 118} staphylococci,^{3, 5, 52, 74, 76} meningococci,¹²⁰ *Bacillus coli* gonococcus,^{22, 113, 96} Gram positive bacilli resembling the Welch bacillus,⁹⁰ and the tubercle bacillus.^{87, 82} A number of cases have been observed in the puerperium,^{82, 106, 107, 108, 110, 119} and a number have been reported after influenzal angina,^{7, 14, 16, 75, 116} and acute articular rheumatism.^{11, 21, 35, 46, 86, 114} It has even been observed after measles⁵⁰ and pertussis.⁹² Not only have different men blamed different bacteria as the etiological agents of the disease, but some have even believed the condition to be due to a protozoan.^{60, 99, 106, 107, 108} Is the disease only a syndrome that can be caused by any one of a number of infective agents?

A few writers have considered the disease to be due not to a microorganism but rather to a form of intoxication. Thus it has been observed in cases of food poisoning,^{93, 94, 95} after exposure to cold,^{36, 82} in gout,⁸² in alcoholic patients,¹¹⁴ and in patients with various gastrointestinal diseases resulting in ulceration of the gastrointestinal tract with possible absorption of toxic products.^{2, 49, 104} Others have believed it to be due to vascular changes in the small arteries.¹¹⁴ With so many conflicting opinions given, we must conclude that at the present time the disease can be attributed to no definite cause.

PATHOLOGY

The pathology of dermatomyositis will be described in great part in the following pages under the description of the disease. It need not be repeated here. It is ⁸² a parenchymatous and interstitial myositis, implicating the entire musculature of the body or a large part of it. A whole muscle may be involved or only a part of it ⁴. Macroscopically there are edema and discoloration of the muscles, which not rarely are also the site of hemorrhages. Waxy degeneration is frequently present ^{11, 58}. The tissues may be so pale and the edema so great that it may be impossible to distinguish muscle from fascia ⁷⁵. Muscle, fascia, and fat—all may have the same appearance. The muscles may have a grayish yellow coloration, they may be speckled, they may be soft, or brittle or even hard. Even calcareous incrustation of necrotic muscle tissue has been observed ⁴⁰. The subcutaneous areolar and fatty tissue may also be edematous, and may likewise be the site of small hemorrhages.

Microscopically there is seen round cell infiltration of the interstitial tissue and thickened perimysium. The nuclei of the sarcolemma may be increased in number, ¹¹ and the muscle fibers greatly swollen—to four or five times their normal diameter—with occasional large vacuoles within the muscle sheath, and numerous small hemorrhages within the intermuscular connective tissue.

SYMPTOMATOLOGY

The disease usually begins with the general symptoms of ill health—listlessness, headache, vertigo, gastric symptoms, and a sense of heaviness in the limbs, or the patient may complain that his limbs feel as if they had grown shorter ⁹⁸. In a few instances a chill has been the initial symptom ¹¹⁴. Soon drawing or tearing pains are felt in the muscles, later the patient becomes tired after walking but a few steps ⁷², and finally the affected muscles gradually become completely incapable of functioning and he lies helpless in bed, unable to move a limb, absolutely quiet—as if in a cast ⁴⁴.

MUSCLE INVOLVEMENT

Any muscle, or any combination of muscles, may be affected. The proximal parts of the extremities are usually more involved than the distal muscles so that the fingers are frequently unaffected at a time when the shoulders and elbows have become immobile ⁸². In a few cases the disease has been limited to only one extremity or even to an individual muscle, ^{81, 89} or various muscles may be affected in succession with disappearance of symptoms in one muscle as new ones are involved ⁵⁷. The cervical dorsal, abdominal, or trunk muscles may be involved, as in our case, ^{88, 93} with resulting rigidity, tenderness, and pain on motion. The muscles of the jaws, ^{17, 16} tongue, ⁸³ soft palate, ^{44, 88} pharynx and larynx may be implicated causing the patient to open his mouth only with difficulty to note that his

tongue is swollen,⁸³ or to have disturbances of speech,^{8, 23, 31, 72, 98, 114} yawning, mastication,³⁷ or, as in our case, even of swallowing^{4, 12, 81, 37, 44, 55, 78, 102} In a few instances the disturbance of deglutition has been the very first symptom of the disease^{55, 114} Regurgitation of food may occur through the nose He may be unable to bring up the secretions that accumulate in his throat⁴⁴ The diaphragm and other respiratory muscles may be affected,^{11, 58, 78, 88} and asphyxia and aspiration bronchopneumonia⁸ are, in fact, the most common cause of death in this disease Rarely asthmatic attacks of short duration have been reported¹¹⁴

In some cases the pains are first felt in the joints, and only later change to the muscles⁸²

There is swelling of the involved muscles and of the soft tissues and skin over them The swelling frequently affects the face, especially in the region of the eyelids The edematous, hard, tense infiltration of the skin and subcutaneous tissues may be so marked that one cannot satisfactorily palpate the underlying muscles to determine their consistency But in some cases the skin is not swollen²⁵ When the muscles can be palpated they sometimes feel hard, sometimes soft and flabby, and even a pseudofluctuation or circumscribed edema or node formation may be present^{34, 85, 98} Sometimes fluid may be aspirated from the muscular swellings⁴ The inflammatory process may extend to the tendon sheaths, and contractures are frequently seen Rarely involuntary muscular twitchings are present⁸¹

Usually the heart muscle is not affected, or at most there exists but a cloudy swelling as a result of septic disease However, this muscle too may participate in the disease process,^{81, 70, 70 00, 120, 5} with resulting grave disturbances of cardiac function,⁸ such as tachycardia independent of the existence of fever, pulse irregularities, dilatation of the right side of the heart⁷⁸ The cardiac condition may even be the cause of death^{82, 114}

SKIN

The skin of the patient with dermatomyositis is usually edematous The edema may be of the soft or hard variety, with or without pitting on pressure^{88, 91} It invariably involves the extremities, being more marked in the proximal than in the distal parts Any portion of the body may be involved as the lips^{51, 114} or penis⁵¹ Or the skin of the entire person may be edematous¹⁰² The face, especially the eyelids, is usually the first part of the skin affected, and the process may advance here to a very marked degree³⁸ before any other symptom of the disease presents itself When redness and warmth are also present, as is frequently the case, one can easily make the mistake of diagnosing erysipelas⁹⁸

There may be present simply an erythema of the skin or scalp,⁴ or there may exist exanthemata resembling the lesions of any one of many kinds of skin diseases roseolar lesions, maculo-papular lesions,⁷⁸ urticaria, blebs, eczema,⁶² morbilliform lesions,⁸³ vesicular lesions¹⁰² which may resemble

varicella⁸³ or lymphangioma circumscriptum, lichen planus,⁷ erythema nodosum, erythema multiforme,³¹ acrodermatitis,^{31, 51, 98} panniculitis with nodules suggestive of erythema nodosum situated deep in the subcutaneous tissue and fat⁸³ The skin may peel^{4, 72, 114} There may be localized swellings,^{14, 51} which may last a long time or disappear within 24 hours, to reappear in a new area Pruritus may or may not be present^{78, 88} The skin may take on a scar-like appearance or even look like that of a patient with scleroderma Or it may be thickened without being edematous^{37, 114} There may be present an extreme hyperesthesia of the thickened skin¹¹⁶ If this thickening occurs in the face, especially if the facial muscles are also involved, the countenance is frequently immobile and like a mask—described by Oppenheim as “alabaster-like” The skin may be glossy, and there may exist a localized^{7, 75, 98} or generalized³⁷ atrophy of it

Hyperhidrosis,^{57, 78} general or localized,³⁸ is frequently present Hair formation may occur in unusual localities⁸², or, on the other hand, loss of hair may result⁵² Dermographia or *tache cerebrale*⁹ may exist Pigmentation of the skin may be marked^{37, 58, 114} Petechiae may be present^{7, 62} or there may be blue spots on the skin suggestive of superficial hematomas in the course of absorption⁵³ Areas of telangiectasia may also be present⁷⁵

Scleroderma-like changes have been noted in a number of instances^{2, 87} Allan's case² is most interesting in that, although eight months after the onset of the dermatomyositis the patient presented the appearance of marked scleroderma with loss of all motion at the elbows, when seen five years later he had almost completely recovered from his disability and the hardness and contracture of the tissues had disappeared

Langmead,⁶¹ Friedman,³¹ and Allan² believed the morbid anatomy in both dermatomyositis and scleroderma to be the same Allan observed that the essential changes in the skin and muscles in both conditions are the edema, cellular infiltration, narrowing or obliteration of the smaller blood vessels, and degeneration of the muscle fibers and skin, followed by fibrous invasion throughout and atrophy

MUCOUS MEMBRANES

Mucous membrane involvement is a frequent occurrence^{34, 48} The nature, extent, and location of the mucous membrane involvement may vary The uvula, palate, and pharynx may be slightly reddened and glassy in appearance,³² or vividly red and beefy^{31, 57} In Steinitz and Steinfeld's case¹⁰³ the saliva was foamy and purulent, interfering with the intake of food and with respiration Laryngeal involvement may give rise to a weak, hoarse, high pitched voice, and to the hawking of blood tinged sputum³⁸ The mucous membranes of the lips and buccal mucosa may be atrophied³⁷ In Joachim's case⁵¹ there was an eruption of “small pimples” at the edge and tip of the tongue and the inner surface of the cheeks There may be an infiltration of the tongue, which on palpation will feel firmer than normal

(reference 103 and Barnes' case reported by Parkes Weber and Gray) The conjunctiva ^{78, 82} and the external auditory canal ⁸² may be involved. The parotids may be swollen and tender ⁴⁸. However, some observers ⁵⁶ have found the mucous membranes of their cases entirely free from involvement.

NERVOUS SYSTEM

The sensorium of the patient usually remains clear until late in the disease, when, as a result of the fever and exhaustion, there may occur mental confusion, hallucinations, and delirium ⁸².

The nerves of special sense are not affected. The sensory nerves are only occasionally involved. The following are symptoms occasionally reported: hyperesthesia of the hands and fingers,³¹ pains in the fingers with a sensation of numbness,^{58, 114} lancinating pains in the hands and feet and tenderness at Erb's point on both sides,⁶⁷ cramp-like pains,¹⁰ pains in the ears and in the abdomen,⁶⁷ intense pain on pressure over the femoral and ulnar nerves,⁹⁸ painful foot spasms with some degree of foot drop,³⁸ pain on slight touch and inability to differentiate between blunt and sharp sensations,⁴⁸ tenderness over the entire skull, especially over the supraorbital regions ³².

The tendon reflexes are decreased or wholly absent if the corresponding muscles are involved by the disease ^{82, 120}. This areflexia may be due to the marked edema, to the inflammatory processes in the muscles, or to a combination of neuritis with the dermatomyositis. On the other hand, accentuation of the deep reflexes has been reported ⁶⁷. A positive Babinski sign has also been observed ⁶².

Because of the resistance which edema offers to the electric current ⁶² it is very difficult, and at times even impossible, to make electrical examinations ⁸². The result is a quantitative decrease or even a complete loss of excitability (particularly to the direct current). Frequently it is impossible to test for electric excitability because of the patient's severe pains ⁶². In mild forms of the disease, however, the reaction to electrical excitability may be entirely normal ⁸².

The skin reflexes may be normal ⁸². A pseudo-Kernig's sign ⁷⁸ has been reported, due probably to infiltration of the extensor muscles of the thighs. Signs similar to those observed in syringomyelia have also been observed ²⁶. Vasomotor symptoms may be present, such as a red or bluish discoloration of a limb, which may be cooler than that on the opposite side ⁶⁷.

In the extremely rare condition known as neuromyositis the neuritic symptoms are prominent, whereas the other manifestations of dermatomyositis, such as marked swelling of the muscles, edema, and exanthema of the skin, are absent. Although the nerve trunks are painful, the involved muscles are not sensitive to touch. There are disturbances of electrical irritability and also sensory disturbances. The reflexes are affected, and vasomotor disturbances are nearly always present. Later on in the disease

atrophic paralysis of muscles with corresponding contractures develops. Thus there may be paralytic contractures in the elbows and finger joints, the hands contracting to the fist position. Histologically in addition to the typical findings of polymyositis there is a destruction of the neurilemma and replacement of nerve fibers by connective tissue. While Steiner¹⁰⁰ believes that neuromyositis is practically always seen in chronic alcoholics and is accompanied by ataxia, Hoegler⁴⁶ reported a case which followed upon an attack of rheumatic pains with swelling of practically all the joints and in which atrophy of the muscles, particularly of the arms, developed after the pain and swelling of the joints disappeared.

The eye muscles may be involved in dermatomyositis. Paralysis of the eye muscles and ptosis,⁸² lateral nystagmus,^{72, 111} and slight exophthalmus without Von Graefe or Stellwag signs,⁴⁴ have been observed. Oppenheim⁸² reported a case in which iritis existed.

SPLEEN, LIVER AND LYMPH GLANDS

Splenic enlargement is frequently reported in dermatomyositis^{9, 14, 31, 35, 57, 58, 103}. The enlargement may be slight,³¹ or the gland may be increased to even twice its normal size.⁸ Van Creveld¹⁴ noted a case in which there was a regression of the enlargement to normal size during a period of temporary improvement. Wasilieu and Eitwid¹¹⁴ reported a case in which the spleen was even smaller than normal.

Some observers have found the liver also enlarged.^{14, 27}

The superficial lymph glands are usually normal, but Fiedler²⁷ reported finding enlarged painful glands, pea-sized or smaller, in the axillary, cervical, and inguinal regions.

OTHER SYMPTOMS

Arthritis is occasionally present. The involvement may be limited to a few joints⁸³ or generalized^{55, 81} and characterized by pain, or swelling, or both.

Hemorrhages from the internal organs, especially intestinal hemorrhages, have been seen¹⁰, and various other gastrointestinal symptoms have been observed in children.⁶²

Loss of weight may be a prominent symptom. One case lost 23 kg (51 lbs) in 12 days.

The temperature is usually elevated.⁶¹ In cases running a chronic course it is not constant, whereas in the acute cases it may go even above 104° F. Schmautzer⁹⁰ was able to show new rises of temperature as new groups of muscles were affected. Cases are known, however, having completely normal temperatures throughout.

LABORATORY FINDINGS

Eosinophilia is frequently observed^{1, 16, 37, 71, 57, 116} counts as high as 76 per cent being reported.²⁷ The eosinophilia may persist even during periods of intermission of the disease.

The urinary findings vary, depending on the presence and degree of nephritis as a complication. The urine may show only a few red blood cells,⁸⁸ or there may be many red cells, casts, and a heavy trace of albumin.⁸³ The total quantity may be markedly diminished.¹⁰³ Urobilin may be present.²⁷ In Joachim's case,⁵¹ although the specific gravity of the urine was 1.032 with no abnormal findings, the urea nitrogen in the blood was 27.2 mg per cent.

An increase of the calcium in the blood to 16.8 mg per cent was observed by Marinesco, Drăganescu and Facon.⁷²

Steinitz and Steinfeld found a disturbance in the creatine metabolism in their case indicated by a permanent creatinuria and diminished elimination of total creatine, by the inability to transform orally administered creatine, and by a diminished creatine content of the muscles. They believe that this disturbance is not a primary symptom of the disease but is caused by grave anatomical changes in the muscles, and that the creatinuria is caused by diminished ability of the muscles to store creatine.

The basal metabolic rate may be normal^{83, 98} or moderately elevated.^{12, 51} It has been observed¹² that early in the disease, before the muscular stiffness becomes prominent, the basal metabolic rate may be elevated even though the clinical picture may resemble that of myxedema, being characterized by mental dullness, drowsiness, dry skin, harsh thin hair, thickening of the hands, pitting edema, and increased sensitiveness to cold.

PROGNOSIS

The prognosis as to life in this disease is very grave. The prognosis is better in the cases that run a mild course early in the disease and in the circumscribed forms.⁸² It is also better in childhood than in adult life.⁶² However, even in severe cases recoveries have been reported.^{10, 13, 21, 33, 35, 48, 49, 65, 69, 77, 106, 107, 108} Oppenheim⁸⁰ in a series of 10 severe diffuse forms of the disease observed five complete recoveries and two deaths. Steiner¹⁰¹ found 17 deaths in a series of 28 collected cases. Sick⁹⁷ reported nine cases in which the diagnosis was established by biopsy of the muscles, with 100 per cent recovery. However, in these cases there was no skin involvement or edema.

The disease may continue for weeks, months, or even years. Weinberger's case¹¹⁵ lasted nine years. Death may result in the early weeks of the disease or after a few weeks complete recovery may occur. In the chronic cases remissions and exacerbations may appear.^{82, 97, 110} One is not justified in considering a case as cured until after the lapse of a number of years. This is because of the possibility of the occurrence of a relapse as in the case of van Creveld who first reported the patient as one that had made a complete recovery,¹⁴ and two years later reported a relapse in the same case.¹⁸

The usual cause of death is bronchopneumonia.¹⁸

DIFFERENTIAL DIAGNOSIS

Polymyositis, or dermatomyositis, is considered by most authorities, though not by all,²⁰ as a different disease from the purulent forms of muscle inflammation. Thus Oppenheim⁸² well says that it is desirable to separate polymyositis from muscle abscess, just as we separate non-purulent encephalitis from brain abscess, in spite of the relation between both latter conditions.

Dermatomyositis so closely resembles trichinosis that it has been called pseudotrachinosis.⁸³ However, one can usually diagnose trichinosis by noting that a number of persons have been affected by the disease and that they all have eaten meat derived from the same animal. Gastrointestinal disturbances are usually present in trichinosis, but in some cases they may be absent. The muscles chiefly involved in trichinosis are the ocular, masticating and laryngeal, and they are the seat of severe pains. Edematous swelling of the face and eyelids develops at an early date in trichinosis. A positive diazo reaction favors the diagnosis of trichinosis, as does also the absence of cutaneous eruptions. As shown above, eosinophilia, which is marked in trichinosis may also be very pronounced in dermatomyositis. Moreover, eosinophilia disappears in trichinosis if mixed bacterial infection develops, it also disappears in grave cases of trichinosis shortly before death.¹⁴ Considerable eosinophilia, furthermore, is found in grave cases of acute muscular rheumatism. Biopsy of a piece of muscle, and the finding of trichinae therein, of course establish the diagnosis.

Mild cases of dermatomyositis may be confused with muscular rheumatism, but the swelling of the muscles, the skin manifestations, the elevation of temperature, and the other phenomena of dermatomyositis, usually enable one easily to make the differentiation.

Polyneuritis may sometimes be difficult to distinguish from dermatomyositis, but the absence of muscular swelling and edema usually facilitate the diagnosis. However, as said before, cases of polymyositis with involvement of the peripheral nerves—called “neuro-myositis”—have been described.^{6, 23, 93, 94} In neuro-myositis ataxia is frequent.

There is a type of dermatomyositis which is limited to one extremity, and which therefore may be confused with plexus neuritis.¹¹⁷

Localized forms of myositis, caused by excessive use or trauma of the part,^{39, 82, 105} may for a time make us suspect a mild form of polymyositis. The condition may lead to a lasting induration and contraction of the muscle, but it has no influence on the general condition of the patient.

An epidemic form of myositic pseudoridity of the neck, produced by painful swelling of some of the neck muscles, has been described.¹⁷ However, the course of events usually easily enables us to make the diagnosis.

Syphilitic myositis also can closely simulate polymyositis.⁴² However, syphilitic myositis usually does not cause such acute myositic symptoms and develops chiefly in the biceps and masseter muscles and less frequently in the pectoralis, deltoid, sternocleidomastoid, or muscles of the calves.¹²⁰

Myositis ossificans, periarteritis nodosa,^{99, 105} nephritis, erythema nodosum, erythema induratum, panniculitis, the "hypodermic type of sarcoid," and scleroderma^{20, 80} may all, also, at times, simulate dermatomyositis. A complete study of such cases, however, reveals their true nature rather easily.

Diffuse exudative scleroderma, in rare cases, does not remain limited to the skin and subcutaneous tissues but involves also muscles and fascia, and causes their atrophy. Muscular atrophies in such cases are not caused by inactivity, but are the result of sclerotic processes in the muscles.⁹⁸ Moreover, in scleroderma there may be an erythematous eruption occurring concurrently with or before the characteristic changes are found, and during the course of the disease fresh eruptions may appear from time to time. During the active phase there may even be edema and fever. All these add to the difficulties of diagnosis. Several observers have noted the association of scleroderma and dermatomyositis.^{47, 44, 87} Bing⁶ and Friedman³¹ reported cases that showed a combination of polymyositis interstitialis, scleroderma, and tendinitis calcarea.

Erysipelas, which dermatomyositis often resembles, can be excluded by the finding of the myositic phenomena such as pains and weakness.⁷²

Early in the course of the disease dermatomyositis may resemble myasthenia gravis. Myasthenia gravis usually, however, runs a long chronic course—even for decades—pains are unusual and insignificant when present in myasthenia gravis, and there is a special weakness of the muscles of the face, whereas dermatomyositis runs an infinitely more rapid course, pains are an outstanding feature, and weakness of the facial muscles is absent.⁸

Oppenheim⁸² has called attention to cases of polymyositis which early in their course suggested the diagnosis of "akinesia algera," spondylitis, or chronic rheumatism.

Urbach¹⁰⁹ described an unusual case under the name of "pseudoleukemic dermatomyositis." It resembled dermatomyositis much in appearance, but the histologic picture of areas of affected skin suggested a diagnosis of lymphoid leukemia, for there was an infiltration almost entirely of lymphocytes. However, the blood and lymph gland examinations did not support the diagnosis of leukemia.

Litten⁶⁶ found in carbon monoxide poisoning that the changes in the muscles resembled those of polymyositis. Blood examination and history will readily, however, differentiate between the two conditions.

Some believe that there is a similarity between the changes found in polymyositis and those in Volkman's ischemic myositis.⁶³ The history in such cases, however, will enable us to make the proper diagnosis.

Dermatomyositis may resemble that type of calcinosis or calcification of the subcutaneous tissue in which there is a sclerosis of the skin and muscle, particularly if the calcinosis is preceded by a papulo-erythematous eruption.⁶¹

TREATMENT

There is no specific treatment for dermatomyositis. Various curative and palliative measures have been suggested by different authors. Oppenheim⁸² advocated diaphoresis followed by thermomassage and electrotherapy, wet packs locally, and a warm climate during convalescence. Others have suggested hot air baths,⁸³ repeated small doses of neosalvarsan,⁵⁵ yatren or yatren-casein injections,³² quinine and ferric chloride,¹⁴ and calcium chloride.⁴⁴ Tonsillectomy has often been done^{9, 15, 16, 18, 31, 55}. However the results following this procedure have been discouraging. Grunke³⁷ employed the Leriche-Brünig's operation on the left brachial artery without any beneficial effect. Stimulation and artificial feeding, as through a tube, are frequently necessary^{57, 88}.

SUMMARY

A case of dermatomyositis with complete autopsy findings is reported. This case is of special interest because of the following: (1) involvement of the esophagus with difficulty in swallowing, (2) ulcerations of the esophagus and large intestine, (3) neurotrophic changes in the nerve ganglia of the gastrointestinal tract, and (4) edema of the larynx and glottis with consequent difficulty in speech.

A discussion of the disease is presented in light of the observations noted in a review of the literature on the subject.

The authors gratefully acknowledge the continuous assistance and stimulation given them by Dr. Meyer A. Rabinowitz throughout the entire preparation of this paper, and they also thank Dr. Max Lederer, of the Department of Pathology, for his help in the preparation of the photographs shown of skin and muscle.

BIBLIOGRAPHY

1. AKERSTEN, Y. Die differentialdiagnostische Deutung der Bluteosinophilie bei Polymyositis und gleichartigen Krankheitszuständen, *Acta med. Scandinav.*, 1931, **144**, 34-42.
2. ALLAN, W. Dermatomyositis or scleroderma?, *Arch. Derm. and Syph.*, 1929, **14**, 265-269.
3. BACIALLI, P. Contribuzione allo studio della patogenesi e delle alterazioni istologiche del tessuto muscolare nella polimiosite acuta primaria, *Policlinico*, 1902, **19**, 16-26.
4. BATTEN, F. E. Case of dermatomyositis in a child, with pathological report, *Brit. Jr. Child Dis.*, 1912, **17**, 247-257.
5. BAUER, J. Ein Fall von acuter hamorrhagischer Polymyositis, *Deutsch. Arch. f. klin. Med.*, 1899, **146**, 95-102.
6. BING, R. Spinale syphilitische Muskelatrophie und syphilitische Polymyositis, *Med. Klin.*, 1909, **5**, 1968-1970.
7. BLUMER, G. Report of a case of dermatomyositis, *Yale Med. Jr.*, 1911, **18**, 31-33.
8. BOLAFFI, A. Dermatomiosite a manifestazioni prevalentemente miasteniche, *Minerva med.* (Pt. 1), 1929, **19**, 303-306.
9. BRONSON, E. (For SUTHERLAND, G. A.) Case of dermatomyositis, *Proc. Roy. Soc. Med.*, 1916-1917, *Sec. Study Dis. Child.*, **10**, 28-32.
10. BUSS, Ein Fall von acuter Dermatomyositis, *Deutsch. med. Wchnschr.*, 1894, **19**, 788-790.
11. CARLEBACH, S. Ein seltener Fall von Polymyositis, *Aerztl. Rundschau*, 1928, **104**, 231-233.

- 12 CARNEY, M. J. A case of chronic dermatomyositis, *Canad Med Assoc Jr*, 1927, xvii, 911-913
- 13 CHRISTFN, W. Ein Fall von Polymyositis acuta, *Cor-Bl f Schweiz Aerzte*, 1903, xxxiii, 822-823
- 14 VAN CREVELD, S. Ein Fall von Polymyositis acuta, *Ztschr f Kinderh*, 1929, xlvii, 74-84
- 15 VAN CREVELD, S. Ein Fall von Polymyositis acuta, *Ztschr f Kinderh*, 1930, xlix, 357-360
- 16 VAN CREVELD, S., and OUWEHAND, P. Case of acute polymyositis, *Nederl Tijdschr v Geneesk*, 1930, lxxiv, 1473-1477
- 17 CURSCHMANN, H. Über eine Epidemie von myositischer Pseudogenickstarre, *München med Wchnschr*, 1917, lxiv, 1-5
- 18 DAVISON, C. Dermatomyositis: a clinicopathologic study, *Arch Derm and Syph*, 1929, xix, 255-264
- 19 DRIMEL, V. C. Di, un caso di Sclerema dei neonati a forma polimiositica, *Arch Ital di dermat sif*, 1928, iv, 81-105
- 20 DIETSCHY, R. Über eine eigentümliche Allgemeinerkrankung mit vorwiegender Beteiligung von Muskulatur und Integument, *Ztschr f klin Med*, 1907, lxiv, 377-399
- 21 EDENHUIZEN, H. Über einen Fall von Polymyositis bei akuter Polyarthritis, *Deutsch Arch f klin Med*, 1906, lxxvii, 14-30
- 22 EICHHORST, H. Über Muskelerkrankungen bei Harnrohrentripper, *Deutsch med Wchnschr*, 1899, xxv, 685-687
- 23 FAJERSZTAJN. Quoted by Oppenheim⁸²
- 24 FEDELI, A. Contributio alla conoscenza della polimiosite, *Gaz d osp*, 1909, xxx, 1081-1083
- 25 FELS, I. Ein Fall von Polymyositis acuta, *Med Klin*, 1918, xiv, 1163-1164
- 26 FERNANDEZ SANZ, E. Polimiositis y siringomielia, *El Siglo med*, 1926, lxxvii, 261-264
- 27 FIEDLER, E. Über einen Fall von chronischer Polymyositis mit hochgradiger Eosinophilie und periodisch wiederkehrenden fieberhaften Exazerbationen, *München med Wchnschr*, 1931, lxxviii, 1176-1177
- 28 FOX, H. Acute polymyositis, *Am Jr Med Sci*, 1913, cxlv, 879-881
- 29 FRAENKEL, A. Über eigenartig verlaufene septikopyämische Erkrankungen nebst Bemerkungen über acute Dermatomyositis, *Deutsch med Wchnschr*, 1894, xx, 193-196, 227-229, 245-249
- 30 FRENCH. Quoted by Parkes Weber and Gray⁸³
- 31 FRIFDMAN, E. D. Dermatomyositis, *Med Jr and Rec*, 1926, cxxiii, 382-386
- 32 VON FRISCH, A. V. Zur Klinik der Dermatomyositis, *Med Klin*, 1927, xliii, 1405-1406
- 33 GFORGIEWSKY. A case of acute hemorrhagic polymyositis, *Bolnitsch Gaz Botkina*, 1901, xii, 696
- 34 SCHENK VON GRYFRN, E. Ein Fall von chronischer Dermatomyositis, *Wien klin Rundschau*, 1910, xxiv, 105-107, 123-125, 137-139, 154-157
- 35 GOTTSTEIN, E. Über Polymyositis, *Deutsch Arch f klin Med*, 1907, xci, 198-211
- 36 GOWERS, W. Über Polymyositis, *Wien med Presse*, 1899, xl, 2172-2179
- 37 GRUNKE, W. Tuberkulose als Ursache einer Dermatomyositis, *Ztschr f klin Med*, 1925, cii, 311-319
- 38 GWYNN, N. C., and GORDEN, W. A case of dermatomyositis which recovered, *Lancet*, 1910, ii, 226-227
- 39 HACHENBRUCH, P. Über interstitielle Myositis und deren Folgezustand, die sogen rheumatische Muskelschwiele, *Beitr z klin Chir*, 1893, x, 73-101
- 40 HAMMES, F. Polymyositis cronica, ein Beitrag zum Symptomenbild derselben, *Med Klin*, 1920, xvi, 876-877
- 41 HEPP, P. Über Pseudotrichinose, eine besondere Form von acuter parenchymatöser Polymyositis, *Berl klin Wchnschr*, 1887, xxiv, 297-299

- 42 HERRICK, J B Polymyositis acuta, with report of a case presumably of syphilitic origin *Am Jr Med Ser*, 1896, cxI, 414-430
- 43 HERZ H Über gutartige Fälle von Dermatomyositis acuta, *Deutsch med Wchnschr*, 1894, xx, 790-793
- 44 HFIN, L G Dermatomyositis, *Jr Am Med Assoc*, 1924, lxxxiI, 1019-1021
- 45 HATEK, J Polymyositis acuta hemorrhagica, *Wien med Presse*, 1905, xliI, 917-925
- 46 HOEGLER, F Ein Fall von chronischer Polyneuromyositis mit hochgradigen Kontrakturen, *Wien Arch f inn Med*, 1921, II, 91-106
- 47 HOOVER, C F Dermatomyositis, in *Tice's Practice of Medicine*, Hagerston, Md, 1921, vi, 536-543
- 48 JACOBY, G W Subacute progressive polymyositis, *Ir Nerv and Ment Dis*, 1888, xI, 697-726
- 49 JANOWSKI, T G, and WISSOKOWICZ, W K Ein Fall von Dermatomyositis, *Deutsch Arch f klin Med*, 1901, lxxI, 493-512
- 50 JESSEN, W, and EDENS, E Polymyositis und Polymyositis bei Morbillen, *Berl klin Wchnschr*, 1904, xli, 847-852
- 51 JOACHIM, H A case of dermatomyositis, *Arch Derm and Syph*, 1923, viI, 326-331
- 52 KANKELEIT Über primäre nichteitrige Polymyositis *Deutsch Arch f klin Med*, 1916, cxx, 335-349
- 53 KARLMARK, E Zur Pathologie der Polymyositis, *Acta med Scandinav*, 1929, lxxviI, 59-64
- 54 KLINGMAN, W O Dermatoneuromyositis resulting in scleroderma, *Arch Neurol and Psych*, 1930, xxiv, 1187-1198
- 55 KROEMER Ein Fall von Dermatomyositis, überraschende Heilung bei Salvarsanbehandlung, *München med Wchnschr*, 1920, lxxviI, 1015-1017
- 56 KORNILOW, A V Polymyositis primaria reuta, *Deutsch Ztschr f Nervenhe*, 1896, ix, 119-138
- 57 KOSTRZEUSKI, J, and BOBRZYNSKI, W Case of dermatomyositis, *Polska gaz lek*, 1930, ix, 44-47
- 58 KRIEGSMANN, G Über primäre Polymyositis, *Arch f Psychiat*, 1927, lxxviI, 360-370
- 59 KUSSMAUL A, and MAIER, R Über eine bisher nicht beschriebene eigentümliche Arterienkrankung (Periarteritis nodosa), die mit Morbus Brighti und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsch Arch f klin Med*, 1866, I, 484-518
- 60 LANDSTEINER, K Über die Aetiologie der Polymyositis, *Svenska Läk-sällsk handl*, 1917, xliii, 759-774
- 61 LANGMEAD, F S The relationship between certain rare diseases—generalized scleroderma calcinosis, dermatomyositis, myositis fibrosa, *Arch Pediat*, 1923, xI, 112-120
- 62 LEHMKUHL, H Ein Fall von Dermatomyositis, *Arch f Kinderh*, 1925, lxxvii, 179-185
- 63 LEPIRE, R Polymyositis, *Rev de med*, 1901, xvi, 426-428
- 64 LEVY-DORN, M Ein seltener Fall von Polymyositis und Neuritis, *Berl klin Wchnschr*, 1895, xxxii, 761-762
- 65 LEWY, B Zur Lehre von der primären acuten Polymyositis, *Berl klin Wchnschr*, 1893, xxx, 420-423, 449-453, 475-477
- 66 LITTEN Discussing a paper by A Fraenkel on Eigenartig verlaufene septico-pyämische Erkrankungen nebst Bemerkungen über die acute Dermatomyositis, *Deutsch med Wchnschr*, 1894, xx, 258
- 67 LOEWENTHAL, S Über Neuro-dermato-myositis, *Schweiz Arch f Neurol u Psych*, 1931, xxviii, 126-132
- 68 LORENZ, H Die Muskelerkrankungen, published as vol xi, pt III, of H Nothnagel's *Handbuch der speziellen Pathologie und Therapie* 1898, Holder, Vienna
- 69 LORENZ, H Die Muskelerkrankungen, 2nd Pt, 1904, p 391, Is vol xi, pt III, of H Nothnagel's *specielle Pathologie und Therapie*, Holder, Vienna

- 70 LORENZ Herzerscheinungen bei der akuten Polymyositis und deren Bedeutung für die Diagnostik der Letztgenannten, *Deutsch med Wchnschr*, 1906, *xxxii*, 777-778
- 71 LUNDQUIST, J Polymyositis, *Acta med Scandnav*, 1929, *lxxii*, 53-58
- 72 MARINESCO, G, DRAGANESCO, S, and FACON, E Contribution à l'étude de la dermatomyosite, *Ann de med*, 1931, *xxx*, 145-162
- 73 MARTINOTTI, C Über Polymyositis acuta, verursacht durch einen Staphylococcus, *Zentralbl f Bakteriologie Parasitenkunde u Infektionskrankheiten*, 1898, *xxiii*, 877-880
- 74 MAYESIMA, J Zur Ätiologie der Polymyositis, *Deutsch Ztschr f Chir*, 1910, *civ*, 321-328
- 75 McLESTER, J S Dermatomyositis, *Trans Assoc Am Phys*, 1926, *xli*, 283-286, also reported in *Jr Am Med Assoc*, 1926, *lxxvii*, 1990
- 76 MOORE, C, and KOCH, L A Dermatomyositis—report of a case with necropsy, *Am Jr Dis Child* 1928, *xxxv*, 71-81
- 77 NGUBAUR, W Ein Fall von akuter Dermatomyositis, *Centralbl f inn Med*, 1899, *xx*, 289-299
- 78 VON NIEDNER Dermatomyositis und infektiöse Muskelerkrankungen, *Deutsch med Wchnschr*, 1920, *xlii*, 570-571
- 79 OPPENHEIM, H Zur Dermatomyositis, *Berl klin Wchnschr*, 1899, *xxxvi*, 805-807
- 80 OPPENHEIM, H Über die Polymyositis, *Berl klin Wchnschr*, 1903, *xl*, 381-416
- 81 OPPENHEIM, H Diseases of the nervous system, a textbook for students and practitioners of medicine Translated and edited by E E Mayer, 2nd Am Ed, 1904, J B Lippincott Co, Philadelphia and London
- 82 OPPENHEIM, H Die Polymyositis acuta und chronica in *Lehrbuch der Nervenkrankheiten*, 7th Ed, Karger, Berlin, p 840-847
- 83 WEBER, F P and GRAY, A M H Chronic relapsing polydermatomyositis with predominant involvement of the subcutaneous fat (panniculitis), *Brit Jr Dermat and Syph*, 1924, *xxxvi*, 544-560
- 84 POTAIN Morve chronique de forme anormale, *Bull et mem Soc med d hop de Paris* 1875, *xii*, 314-318
- 85 PRINZING, A Ein Fall von Polymyositis acuta hemorrhagica, *München med Wchnschr*, 1890, *xxvii*, 846-849
- 86 RISSE, H Polymyositis acuta und acuter Gelenkrheumatismus, *Deutsch med Wchnschr*, 1897, *xxiii*, 232-234
- 87 ROSENTHAL, C, and HOFFMAN, H Ein Fall von Dermatoneuromyositis, *Klin Wchnschr*, 1924, *iii*, 115-116
- 88 SCHILL E Über einen Fall von Polymyositis, *Wien Arch f inn Med*, 1926, *xii*, 353-360
- 89 SCHLESINGER, H Zur Lehre von der hamorrhagischen Myositis, *Wien klin Rundschau*, 1899, *xiii*, 433-435
- 90 SCHMAUTZER J Über Polymyositis acuta, *Med Klin*, 1914, *x*, 281-283
- 91 SCHNELL C Über Polymyositis, 1892, J M Richter, Würzburg
- 92 SCHUELLER, A Polymyositis im Kindesalter, *Jahrb f Kinderh*, 1903, *lviii*, 193-217
- 93 SENATOR H Über acute multiple Myositis bei Neuritis, *Deutsch med Wchnschr*, 1888, *xiv*, 449-450
- 94 SENATOR H Über acute und subacute multiple Neuritis und Myositis, *Ztschr f klin Med*, 1889, *xv*, 61-81
- 95 SENATOR, H Über acute Polymyositis und Neuromyositis, *Deutsch med Wchnschr*, 1893, *xi*, 933-936
- 96 SERVEL These de Bordeaux, 1900
- 97 SICK, K Akute rezidivierende Polymyositis in epidemischem Auftreten, *München med Wchnschr*, 1905, *li*, 1092-1095, 1152-1155
- 98 SLUCZEWSKI A Über einen Fall von Dermatoneuromyositis, *Derm Ztschr*, 1931, *lx*, 390-395

- 99 SMITH T Quoted by Oppenheim ⁸²
- 100 STEINER W R Non-suppurative myositis, in OSLFR, W, and McCRAE, T Modern medicine, Vol 1 2d Ed, 1915, Lea and Febiger, Philadelphia and New York, pp 875-880
- 101 STEINER, W R Quoted by OSLFR Principles and Practice of Medicine, 8th Ed, 1918, D Appleton and Co, New York pp 1128-1129
- 102 STEINER, W Dermatomyositis with report of two cases, Jr Am Med Assoc, 1922, LVIII, 271-273
- 103 STEINITZ, H, and STEINFELD, F Untersuchungen zum Kreatinstoffwechsel bei Dermatomyositis, Ztschr f d ges exper Med, 1931, LXXX, 319-328
- 104 STERTZ Polymyositis, Berl klin Wchnschr, 1916, LIII, 489
- 105 STRUMPFLL, A Zur Kenntniss der primären acuten Polymyositis, Deutsch Ztschr f Nervenl, 1891, 1, 479-505
- 106 UNVERRICHT, H Über eine eigenthümliche Form von akuter Muskelentzündung mit einem der Trichinose ähnelnden Krankheitsbilde, Cor-Bl d allg ärztl Ver v Thüringen, 1887, VII, 207-219
- 107 UNVERRICHT, H Polymyositis acuter progressiva, Ztschr f klin Med, 1887, VII, 533-549
- 108 UNVERRICHT, H Über eine eigenthümliche Form von acuter Muskelentzündung mit einem der Trichinose ähnelnden Krankheitsbilde, München med Wchnschr, 1887, XXXIV, 488-492
- 109 URBACH, E Dermatomyositis pseudoleucaemica, Arch f Dermat u Syph, 1930, CLXII, 27-39
- 110 WAETZOLDT Beitrag zur Lehre von der Polymyositis acuta (post partum), Ztschr f klin Med, 1893 XXII, 600-625
- 111 WAGNER E Fall einer seltenen Muskelkrankheit, Arch f Heilkunde, 1863, IV, 282-283
- 112 WAGNER, E Ein Fall von acuter Polymyositis, Deutsch Arch f klin Med, 1886-1887, VI, 241-266
- 113 WARE, M W Gonorrheal myositis, Am Jr Med Sci, 1901, CXXII 40-45
- 114 WASILIEU, V M, and EITWID, A A Case of dermatomyositis, Russk Klin, 1928, X, 584-595
- 115 WEINBERGER Quoted by Wermer ¹¹⁶
- 116 WERMER, P Ein Fall von primär chronischer Dermatomyositis, Wien med Wchnschr, 1927, LXXVII, 1759
- 117 WERTHEIM-SALOMONSON Pathologie en therapie der neuritis, myositis, zenuwgezwellen, neuralgie en myologie, Amsterdam, 1911
- 118 VON WIESNER, R R Über Polymyositis acuta-gleichzeitig ein Beitrag zur Kenntniss der Infektion mit *Streptococcus pleomorphicus*, Mitteil a d Grenzgeb d Med u Chir, 1918-1919, XXXI, 1-11
- 119 WINKEL, F Ein eigenthümlicher Fall von Polymyositis parenchymatosa puerperalis mit Neuritis interstitialis, Centralbl f Gynak, 1878, II 145-150
- 120 VON ZALKA, E Über einen seltsamen Fall von Polymyositis, Virchow's Arch f path Anat, 1931, cclXXXI, 114-128

FATAL DIABETIC COMA WITH ACUTE RENAL FAILURE¹

By MAYNARD E. HOLMES, M D , F A C P , *Syracuse, New York*

SEVERAL observers have called attention to the presence of impairment of renal function in diabetic coma. Fitz¹ in 1917 demonstrated that some degree of kidney insufficiency accompanied nearly all cases of severe diabetic acidosis. Joslin² states that in diabetic coma oliguria and moderate nitrogen retention are common but that anuria occurs only occasionally. Waiburg³ in an admirable review of this subject emphasizes the fact that it is not generally recognized that kidney function may become very deficient in diabetic acidosis. In 1931 Labbe and Boulin,⁴ after a careful review of the literature on the subject, were able to collect only 16 cases of undoubted diabetic coma with blood urea retention of over 100 mg per 100 c c. To this number Lyall and Anderson⁵ in 1932 added six cases, making a total of 22 instances of diabetic coma with urea retention of over 100 mg per cent, observed by fewer than 20 workers. Of the original 22 cases 14 ended fatally, and in the same series there were but six deaths among 29 cases with blood urea retention of less than 100 mg per 100 c c. Joslin⁶ reports five cases of diabetic acidosis with blood non-protein-nitrogen retention of over 100 mg per cent with three fatalities.

The material presented here covers five cases of fatal diabetic coma all with blood non-protein-nitrogen retention of over 100 mg per cent, observed in the past five years. All of these cases fell properly in the class of diabetic acidosis as judged by the usual clinical and laboratory criteria, namely, excessive hyperglycemia, reduction of the alkali reserve of the plasma, glycosuria and ketonuria. All were known diabetics and were under observation during their fatal illness for from two to eight days. The ages were from 11 to 55 years. In none of the cases was there evidence of pre-existing renal involvement. Respiratory infection was present in all of the cases during their illness, and while it undoubtedly was a factor in precipitating the acidosis, it did not seem to be concerned in the production of the course of events which led to the fatal termination. The temperature was normal in each case upon entrance to the hospital. All cases were handled in a similar manner, insulin was given at one to six hour intervals, carbohydrate was administered in the form of orange juice, ginger ale or grape juice by mouth, or subcutaneously in 5 per cent dextrose solution or intravenously in 10 to 50 per cent solution. Water by mouth and normal saline

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935

From the Department of Medicine, University Hospital, Syracuse University School of Medicine

parenterally were given as additional fluids. Alkali was given in two cases. A résumé of the important laboratory, clinical and treatment data is given in the accompanying charts. Blood sugar determinations were made by the Folin Wu method, blood plasma carbon dioxide combining power by the Van Slyke technic, non-protein-nitrogen of the blood as outlined by Folin, urine sugar by the Benedict method and the ketone bodies by the nitroprusside and ferric chloride tests.

The striking features of this group of cases were the failure of the acidosis as exemplified by the plasma carbon dioxide combining power to clear in response to insulin therapy, and the development of evidence of renal insufficiency. The carbon dioxide combining power always remained below 30 volumes per cent despite the lowering of the blood sugar and the clearing of the ketonuria. All patients seemed to respond favorably to treatment at first and all revived for a brief period a few hours after treatment was begun, only to lapse back into a fatal stupor, and finally died in apparent uremia. Oliguria was noted in all cases and anuria, for from 6 to 22 hours.

TABLE I (Case 1)

Case 1	Urine					Blood		
Date March 1929	Sugar	Acetone	Diacetic acid	Albumin	Casts R b c	Sugar Mg per cent	N P N Mg per cent	CO. vol per cent
1	++++	++++	+	++	++	444	49	10
2	+	+		+++	+++	390		10
3	+			+++	+++	160	148	10
4	+							10

Case 1	Urine	Treatment					Comment
		Fluid intake c c	Carb Gm	Insulin units	NaHCO ₃ Gm	NaCl Gm	
Date March 1929	Vol- ume c c						Female, aged 18 Diabetes few wks Ill 3 days Stupor 12 hours
1	2205	5600	129	220		22	B P 102/90 Temp 98.8° F Emesis 240 c c
2	563	4800	242	135	25	10	Talked in a m Emesis 480 c c B P 160/90
3	244	6680	403	60	42	48	Talked to family B P 134/60 Anuria 12 hours Edema noted Coma late in day
4	0	2000	177	35			B P 146/42 Coma and anuria Edema marked Died 9 a m

TABLE II (Case 2)

Case 2	Urine					Blood		
	Sugar	Acetone	Diacetic acid	Casts R b c	Albumin	Sugar Mg per cent	N P N Mg per cent	CO ₂ Vol per cent
12	++++	++++	++			412	45	10
13	+	0	0		++	153		
14	+					208		
15	++	0	0	++	+++	216		14
16	++							
17	++			+++	+++		120	16

Case 2	Urine	Treatment					Comment
		Fluid Intake c c	Carb Gm	Insulin units	NaCO ₃ Gm	NaCl Gm	
Date Febr 1929	Volume c c						Female, aged 29 mos Ill 48 hours Diabetes 3 Coma 13 hours
12	600	5460	94	110		27	Temp 97° F Anuria 11 hours
13	390	5370	370	60			Emesis 810 c c B P 90/70, 110/70
14	510	2385	244	40	8		Emesis 480 c c
15	630	2550	200	40	24		Brighter Talked
16	390	1750	130	30	8		Refused food Stupor
17	180	2250	104	80		18	Can not arouse Died 4 p m

in four individuals. Casts and red and white blood cells were present in the urine of all patients. Albuminuria, although slight at first, increased as the coma progressed. The non-protein-nitrogen of the blood, while not markedly elevated early, gradually mounted in each case until before death it exceeded 100 mg per 100 c c. In case 5, the blood non-protein-nitrogen was 300 mg per cent on the eighth day which, I believe, is higher than that in any similar case as yet reported. Edema was noted in three instances toward the end, and convulsions (hypoglycemia not present) developed in one patient.

While moderate amounts of acetone were present in the urine of all cases, diacetic acid was absent in one and present only in small amounts in the urine of the other four patients. Warburg³ calls attention to the fact that in cases of this type hyperglycemia may be marked and glycosuria and ketonuria slight, caused apparently by impairment of kidney function. Coburn⁸

TABLE III (Case 3)

Case 3	Urine					Blood		
	Sugar	Acetone	Diacetic acid	Casts R b c	Albumin	Sugar Mg per cent	N P N Mg per cent	CO ₂ vol per cent
30	++++	+++	0	+++	+++			
31	++++	+	0	+++	+++	395	105	15

Case 3	Urine	Treatment				Comment
		Fluid intake c c	Carb Gm	Insulin units	NaCl Gm	
Date Jan 1934	Volume c c					Male aged 28 Diabetes several months Ill 4 days
30	105	3260	47	120	18	Temp 97.6° F Anuria after 11 p m
31	0	2950	51	0	18	Anuria Died 8 a m

has also stressed the point that severe ketonemia may be present despite the absence of acetone bodies in the urine. In Rabinowitch's⁹ case, however, the blood serum gave a negative response to the Wishart test for acetone. Starr and Fitz,¹⁰ and Bock¹¹ report the presence of some unidentified organic acid in the blood of cases of diabetic coma in which the plasma CO₂ combining power fails to rise under adequate insulin therapy, a non-ketone acidosis. Values for the blood non-protein-nitrogen and other evidence of renal involvement were not given for these cases.

The increase in the blood non-protein-nitrogen is probably not entirely an index of failure of kidney function since concentration of the chemical constituents including urea is brought about by dehydration always present in severe diabetic coma. However in this series, the grade of nitrogen retention was much greater than that reported¹³ as a result of dehydration, and the retention occurred late after the anhydremia had apparently been overcome by the administration of large amounts of fluids. The presence of oliguria, anuria, albumin, casts and red blood cells in the urine, edema, and in one patient convulsions can leave little doubt that the severe azotemia in these cases was due to direct retention as a result of acute functional renal failure.

Several factors have been suggested as being concerned in the development of this type of renal failure: (1) shock, (2) dehydration, (3) disturbance of the plasma electrolytes, (4) increased destruction of endogenous protein, (5) insulin and (6) pathologic change in the kidney. Most of these factors are probably interrelated.

Shock in various degrees of severity accompanies all cases of severe

TABLE IV (Case 4)

Case 4	Urine					Blood		
	Sugar	Acetone	Diacetic acid	Albumin	Casts R b c	Sugar Mg per cent	N P N Mg per cent	CO ₂ vol per cent
8	++++	+++	+	++	+	480		
9	++			+++	+	400	103	21
10	++	0	+	+++	++	182	120	
11	++					206	114	22

Case 4	Urine	Treatment				Comment
		Fluid intake c c	Carb Gm	Insulin units	NaCl Gm	
Date Sept 1932	Volume c c					Female, aged 55 Diabetes 4 yrs, on insulin ill and no insulin 4 days Coma 18 hours
8	150	3380	145	290	27	Temp 97.4° F No edema Anuria 12 hours 500 c c 10 per cent dextrose by vein
9	105	4100	75	230	36	B P 140/70 Edema noted Anuria 10 hours 750 c c 10 per cent dextrose by vein
10	112	4600	200	180	39	B P 140/80 Emesis 90 c c Anuria 22 hours 300 c c 25 per cent dextrose by vein Edema increased
11	510	3500	200	130	27	B P 140/80 Voided 510 c c after 11 p m 300 c c 25 per cent dextrose by vein Edema marked Died 2 a m Sept 12

diabetic coma Dehydration, caused by loss of fluids and electrolytes from the blood, produces a condition of hemoconcentration The resultant diminished blood volume, lowered blood pressure and capillary stasis combine to produce a condition of general vasomotor collapse¹² Failure of the capillary circulation of the kidney follows with impairment of renal function, oliguria, anuria, and finally nitrogen retention

That nitrogen retention may occur as a result of dehydration incident to low fluid intake, and excessive loss of fluid by polyuria, vomiting, sweating and hyperpnea, has been demonstrated by Bulger and Peters¹³ Further loss of fluids may occur by transudation from the blood vessels into the tissues¹⁴ Additional evidence that azotemia may be related to disturbance of the blood electrolyte are the observations of Blum,¹⁵ who in two cases of diabetic coma after partial recovery was able to produce marked nitrogen retention by restricting the chloride intake for six days When salt was

TABLE V (Case 5)

Case 5 Date March 1931	Urine					Blood		
	Sugar	Acetone	Diacetic acid	Casts R b c	Albumin	Sugar Mg per cent	N P N Mg per cent	CO. vol per cent
26	++++	++++	++	++	++	440	39	30
27	+	+	+			230		
28	+	+	+	++	++++	133	99	
29	+							
30	++			++				
31	++					487 160	114	29
1	++			++	++++	542 96	171	20
2	++				++++	160 90	223 300	9

Case 5 Date March 1931	Urine Vol- ume c c	Treatment				Comment
		Fluid intake c c	Carb Gm	Insulin units	NaCl Gm	
						Female, aged 11 Diabetes 4 yrs, on insulin Ill and no insulin 1 week
26	75	2290	146	50	16	Stupor 12 hrs Temp 97° F
27	34	2840	112	60	9	Emesis 400 c c
28	165	3160	117	0	18	Answers questions 50 c c 25 per cent dextrose by vein
29	120	1265	70	20		Myringotomy, emesis 60 c c Hungry edema noted 50 c c 25 per cent dextrose by vein
30	225	2215	104	25	14	Emesis 120 c c, edema noted
31	165	1610	100	35	14	B P 125/100, convulsions Spinal fluid negative 50 c c 25 per cent dextrose by vein
1	225	775	63	20	7	Convulsions, edema marked 25 c c 25 per cent dextrose by vein
2	210	50	25	15		50 c c 25 per cent dextrose by vein Edema marked Died 3 a m Apr 3

again administered, the blood urea was restored to a normal level. In a third case under the same régime he was unable to produce azotemia. Depletion of the blood chlorides has been noted in diabetic acidosis. Peters¹⁶ emphasizes that in severe diabetic toxemia the salt content of the blood may be seriously depleted by the loss of chloride to furnish base to neutralize the organic acids present. There is also increased excretion of salt in the urine because of the severe glycosuria.¹² Hartmann¹⁷ believes that in the presence of hypochloremia there occurs an increase in the non electrolyte urea to compensate osmotically for the loss of chloride and carbonate from the blood. Hypochloremia, however, apparently is not a constant finding in diabetic coma with acute renal block, as the cases reported by Fitz,¹ Bulger and Peters,¹³ Fullerton¹⁸ and Lyall and Anderson⁵ revealed normal or increased blood chloride levels. While hypochloremia may occasionally be the primary cause in the production of azotemia in severe diabetic coma, it probably is more commonly concerned only as it contributes to the general state of dehydration.

Excessive breakdown of endogenous protein is said to occur in diabetic acidosis.⁵ Atchley¹⁹ noted increased nitrogen excretion in his cases following the withdrawal of insulin. Dehydration which is present in all cases of severe diabetic coma is often accompanied by marked destruction of body protoplasm.^{20, 21} This process may be concerned in the production of azotemia in severe diabetic acidosis in the same manner that it is believed to cause nitrogen retention in high intestinal obstruction.

There are many points of similarity between diabetic coma with acute renal failure and the toxemia of high intestinal obstruction. Shock, vomiting, dehydration, oliguria, anuria, nitrogen retention and hypochloremia have been noted in both conditions. The same processes believed to be concerned in the production of the azotemia of obstruction may also be operating in severe diabetic acidosis.

The possibility that insulin may be a factor in the production of nitrogen retention in diabetic coma has been suggested by Joslin² and by Bayer²² who reports a fatal case receiving 1145 units during six and a half days. However, the more commonplace explanation is that these large doses were necessary because of the extreme grade of the acidosis present and that it is in such cases that nitrogen retention is most likely to occur. Moreover, urea retention was noted in fatal cases of diabetic coma before insulin was introduced.¹

That some degree of nephropathy is present in the majority of instances of diabetic coma is indicated by the presence of albumin, casts and red blood cells in the urine. Actual parenchymal renal damage probably results from the excessive excretion of ketones, acids and other metabolites. MacNider²³ demonstrated in dogs that the introduction into the blood of either acid or alkali in amounts sufficient to alter the physico-chemical state of the blood to a degree that readjustment was impossible, caused severe renal insufficiency to develop, and the kidneys at autopsy revealed changes similar to

those reported in fatal diabetic coma with acute renal failure. The pathologic changes found in the kidneys of patients dying of diabetic acidosis with renal insufficiency have been described by Warburg,³ Snapper,²⁴ Labbe,⁴ Bayer,²² and Kraus.²⁵ The lesions found have been designated as a nephrosis and also as an early acute nephritis, the kidneys are large and pale with edema of the stroma, and degenerative changes in the tubular epithelium are a prominent feature. Coburn⁸ found no evident renal change in two of his cases which came to autopsy, these cases were observed only a few hours, and evidence of nitrogen retention or of the urinary findings of renal disease was not given. Joslin⁶ reports two fatal cases of this type with multiple abscesses of the kidney.

The treatment of diabetic coma with acute renal failure is likely to be discouraging in the majority of instances especially if nitrogen retention of any marked degree is present. Coburn⁸ emphasizes the importance of blood transfusion and of the intravenous administration of hypertonic solutions of glucose and alkali. Fullerton¹⁸ reports a case with a blood urea above 100 mg per cent that recovered after the administration of hypertonic dextrose solution intravenously. In case 4 of this series after anuria of 22 hours, there was an excretion of 510 c c of urine on the final day apparently as a result of the giving of hypertonic dextrose solution by vein, but in case 5 it had little or no effect. Root²⁶ successfully treated three cases with blood non-protein-nitrogen retention of over 100 mg per cent, with hypertonic salt solution intravenously. He believes that hypochloremia is an important causative factor in this condition, although in one case recorded the blood chlorides were 463 mg per cent. John⁷ describes a case with severe azotemia that recovered after the administration of Fisher's solution by vein. The use of alkali has been advocated in diabetic coma by Starr and Fitz,¹⁰ Bock,¹¹ Hartmann,²⁸ Marriott,²⁹ Bowen³⁰ and others, and its use opposed by Joslin,⁶ Peters,¹⁶ Lemann³¹ and others. In cases 1 and 2 of this series alkali was given but without apparent effect either clinically or chemically. Present experience would seem to indicate that oliguria, anuria and nitrogen retention in diabetic coma can best be combated by overcoming the dehydration and hemoconcentration present with large amounts of normal saline given in part intravenously. Hypertonic salt solution should be administered by vein especially if hypochloremia is present and intravenous infusions of hypertonic dextrose solution given particularly if hyperglycemia is not marked. In the presence of hypotension and shock, fluids and insulin should for the most part be given by vein. When other methods fail to relieve shock and anuria there is justification for the use of blood transfusion.¹⁵

SUMMARY

Five cases of fatal diabetic coma with acute functional renal failure have been reported, with clinical, laboratory and treatment data. The possible explanations for this type of kidney insufficiency have been discussed.

Its development would seem to depend on the following sequence of events, depletion of water and electrolyte from the blood incident to diabetic acidosis, bringing about a condition of dehydration and hemoconcentration with diminished blood volume and hypotension. A state of so-called shock follows with failure of the capillary circulation of the kidney, impairment of renal function, oliguria, anuria, and finally nitrogen retention. In the cases with nitrogen retention of any marked degree actual pathologic changes in the kidney parenchyma develop and become the important factor in the insufficiency. The prognosis in diabetic coma with marked nitrogen retention must be guarded, some patients will recover after exhibiting symptoms of uremia while others progress to a fatal termination in spite of all treatment.

For permission to report these cases the author is indebted to Dr. Edward C. Reifenshien, Professor of Medicine and Director of the Medical Service of the University Hospital, Syracuse University School of Medicine.

BIBLIOGRAPHY

- 1 FITZ, R. Observations on kidney function in diabetes mellitus, *Arch Int Med* 1917, **xx**, 809-827.
- 2 JOSLIN, E. P. The treatment of diabetes mellitus, 4th ed., 1928, Lea and Febiger, Philadelphia.
- 3 WARBURG, E. Diabetic coma complicated with uremia, early history of diabetic coma, *Acta med Scandinav*, 1925, **lxi**, 301-334.
- 4 LABBE, M., and BOULIN, R. Les modifications de l'urée du sang au cours du coma diabétique, *Ann de med*, 1931, **xxix**, 386-409.
- 5 LYALL, A., and ANDERSON, A. G. Diabetic coma, significance of alteration in blood-urea, *Quart Jr Med*, 1932, **i**, 353-360.
- 6 JOSLIN, E. P., and others. Diabetic coma, *Med Clin N Am*, 1929, **xiii**, 11-40.
- 7 MARBLE, A., ROOT, H. F., and WHITE, P. Diabetic coma, *New England Jr Med*, 1935, **ccxii**, 288-297.
- 8 COBURN, A. F. Diabetic ketosis and functional renal insufficiency, *Am Jr Med Sci*, 1930, **clxxx**, 178-192.
- 9 RABINOWITCH, I. M. Kidneys in diabetic coma, *Canad Med Assoc Jr*, 1929, **xxi**, 274-276.
- 10 STARR, P., and FITZ, R. Excretion of organic acids in the urine of patients with diabetes mellitus, *Arch Int Med*, 1924, **xxxiii**, 97-108.
- 11 BOCK, A. V., FIELD, H., and ADAIR, G. S. Acid-base equilibrium in diabetic coma, being a study of 5 cases treated with insulin, *Jr Metab Res*, 1924, **iv**, 27-64.
- 12 ATCHLEY, D. W. Dehydration and medical shock, *Bull New York Acad Med*, 1934, **x**, 138-150.
- 13 BUIGER, H. A., and PETERS, J. P. Concentration of the blood and urine in diabetic toxemia, *Arch Int Med*, 1925, **xxvi**, 857-873.
- 14 PETERS, J. P., KYDD, D. M., and EISENMAN, A. J. Serum proteins in diabetic acidosis, *Jr Clin Invest*, 1933, **xii**, 355-376.
- 15 BLUM, L., GRABAR, P., and VAN CAULAERT. L'azotémie par manque de sel dans le diabète grave, *Ann de med*, 1929, **xxv**, 23-33.
- 16 PETERS, J. P., and others. Total acid-base equilibrium of plasma in health and disease, studies of diabetes, *Jr Clin Invest*, 1925, **ii**, 167-211.
- 17 HARTMAN, A. F., and DARROW, D. C. Chemical changes occurring in body as result of certain diseases in infants and children, acute hemorrhagic nephritis, subacute nephritis, severe chronic nephritis, *Jr Clin Invest*, 1928, **vi**, 127-157.

- 18 FULLERTON, H W, LYALL, A, and DAVIDSON, L S P Treatment of diabetic uremia with hypertonic glucose solutions, *Lancet*, 1932, i, 558-560
- 19 ATCHLEY, D W, and others On diabetic acidosis, detailed study of electrolyte balances following withdrawal and reestablishment of insulin therapy, *Jr Clin Invest*, 1933, xii, 297-326
- 20 GAMBLE, J L Dehydration, *New England Jr Med*, 1929, cci, 909-917
- 21 BACON, D K, ANSLOW, R E, and EPPICER, H H Intestinal obstruction, *Arch Surg*, 1921, iii, 641-654
- 22 BAYFR, L M Six fatal cases of diabetic acidosis, with special reference to occurrence of acute pancreatic necrosis in one and severe nephrosis in another, *Am Jr Med Sci*, 1930, clxxix, 671-683
- 23 MACNIDER, W DE B Studies concerning influence of disturbance in acid-base equilibrium of blood on renal function and pathology, *Jr Metab Res*, 1923, iii, 511-582
- 24 SNAPPER, I Role of kidney in non-renal disorders, *Proc Royal Soc Med*, 1928, xxi, 73-76
- 25 KRAUS, E J, and SELYF, H Über die Veränderungen der Niere beim Insulinbehandelten Coma diabeticum mit Ausgang in Uramie, *Klin Wchnschr*, 1928, vii, 1627-1630
- 26 ROOT, H F Anuria following diabetic coma relieved by hypertonic salt solution, *Jr Am Med Assoc*, 1934, ciii, 482-483
- 27 JOHN, H J Diabetic coma complicated by acute retention of urine, *Jr Am Med Assoc*, 1925, lxxxiv, 1400-1401
- 28 HARTMANN, A F, and DARROW, D C Chemical changes occurring in body as result of certain diseases, composition of plasma in severe diabetic acidosis and changes taking place during recovery, *Jr Clin Invest*, 1928, vi, 257-276
- 29 MARRIOTT, M, and HARTMANN, A F Newer aspect of acidosis, *Jr Am Med Assoc*, 1928, xci, 1675-1679
- 30 BOWEN, B D, and HEKIMIAN, I Diabetic coma, report of 81 instances, *ANN INT MED*, 1930, iii, 1104-1111
- 31 LEMANN, I I Futility of alkali treatment in diabetic coma, analysis of 47 cases, *Am Jr Med Sci*, 1930, clxxx 266-271

INCIDENCE AND SIGNIFICANCE OF THE ROENTGENOLOGIC NICHE IN DUODENAL ULCER *

By B R KIRKLIN, M D , F A C P , and H A BURCH, M D ,
Rochester, Minnesota

IN 1911, at the fortieth assembly of the German Surgical Society, Martin Haudek mentioned the niche as one of the roentgenologic signs of duodenal ulcer, and in a formal paper published in 1912 he cited among several cases four in which niches were demonstrated. In these cases the crater of the ulcer was depicted by a small deposit of bismuth which could scarcely be displaced by manipulation and corresponded to a point on the abdomen that was sensitive to pressure. Although his descriptions and drawings were convincing, the new sign of duodenal ulcer apparently received little attention, and the diagnosis continued to be based chiefly on clinical symptoms in combination with roentgenologic signs of hypermotility and other secondary manifestations. In 1914, Lewis Gregory Cole placed the diagnosis on the logical, practical, and substantial basis of bulbar deformity caused by induration or cicatricial contraction resulting from the ulcer. On that occasion he said also that in some instances the bismuth-filled crater of the ulcer could be seen in profile or face. But distortion of the bulb proved to be such a constant and reliable sign that most examiners still regarded the niche as a mildly interesting but relatively unimportant detail.

Not until 1923, when Akerlund reported an incidence of 60 per cent of niches in more than 100 cases of duodenal ulcer, was this sign given more than passing consideration. Since then various computations as to the frequency with which a niche can be demonstrated have appeared, such as those of Diamond, 66.6 per cent, Carman and Sutherland, 13.27 per cent, Berg, 50 per cent, Albrecht, 90 per cent, Akerlund, 75 per cent (in 1931), Kirklin, 15.24 per cent, Geyman, 64 per cent, Clark and Geyman, 54 per cent, Ettinger and Davis, 50 per cent. For comparison with these estimates we have again reviewed the records of this clinic for the 15 months ending March 31, 1935. During that period duodenal ulcer was diagnosed roentgenologically in 1,489 cases, and the presence of a niche was noted in only 264, or 17.7 per cent. The marked discordance in these statistics led us to inquire further into the problem of incidence, not with the expectation of solving it decisively, but with the hope of finding probable reasons for some of the discrepancies.

Diverse conceptions of the criteria by which the niche should be judged probably underlie the entire disparity of incidence. It is generally agreed that, depending on the angle of view, niches may be marginal (figure 1) or central (figures 2 and 3), that they are more often situated on the mesial

* Read before the Philadelphia meeting of the American College of Physicians, May 1, 1935.

From The Mayo Clinic, Rochester, Minnesota

border or posterior or anterior wall of the bulb but may occur in the base or lateral wall or in the descending portion of the duodenum (figure 4), that usually they are small, with a diameter from one or two mm to one cm, that they may be hemispherical, angular or irregular in profile, and that an individual niche should maintain the same site and form during the examination and at reexamination. To these characteristics we would add, as would other examiners who depend primarily on roentgenoscopy for diagnosis, that the deposit of barium in the crater should persist for a time, not only when the bulb is evacuated spontaneously or by steady pressure, but also and especially when the bulb is subjected to palpatory manipulation.



FIG 1 Marginal niche on lesser curvature side of bulb

This immediately brings up the collateral question as to the technic that should be employed. Most of those examiners who have found a high percentage of niches employ roentgenography with the well known compression apparatus as a routine, and they insist that many small niches will otherwise escape roentgenoscopic observation. But, even if it is conceded that roentgenograms will depict minute niches that cannot be seen on the fluoroscopic screen, the roentgenographic method introduces a new factor of error in the opposite direction. In the many cases of duodenal ulcer, whether temporarily healed or active and with or without a definite crater, in which the bulb presents multiple spastic or cicatricial sacculations or a pseudodiverticulum, any or all of the pouches may retain barium under the steady pressure employed in the roentgenographic method and may be mistaken for

niches. Moreover, by this method a small aggregation of barium may be pent up in the pyloric canal or in the mucosal folds of a normal bulb and thus simulate a niche. On the other hand, by roentgenoscopy with manipulation, practically all pseudoniches can be emptied and by this feature distinguished from true niches.

At the clinic, compression roentgenography is often employed to depict duodenal niches and other phenomena of which a permanent record is desired. In our hands this method has not as yet disclosed any niche which had not been discerned roentgenoscopically. However, any examiner who is at all doubtful as to the reliability of his roentgenoscopic technic is quite justified in using compression roentgenography as a routine.

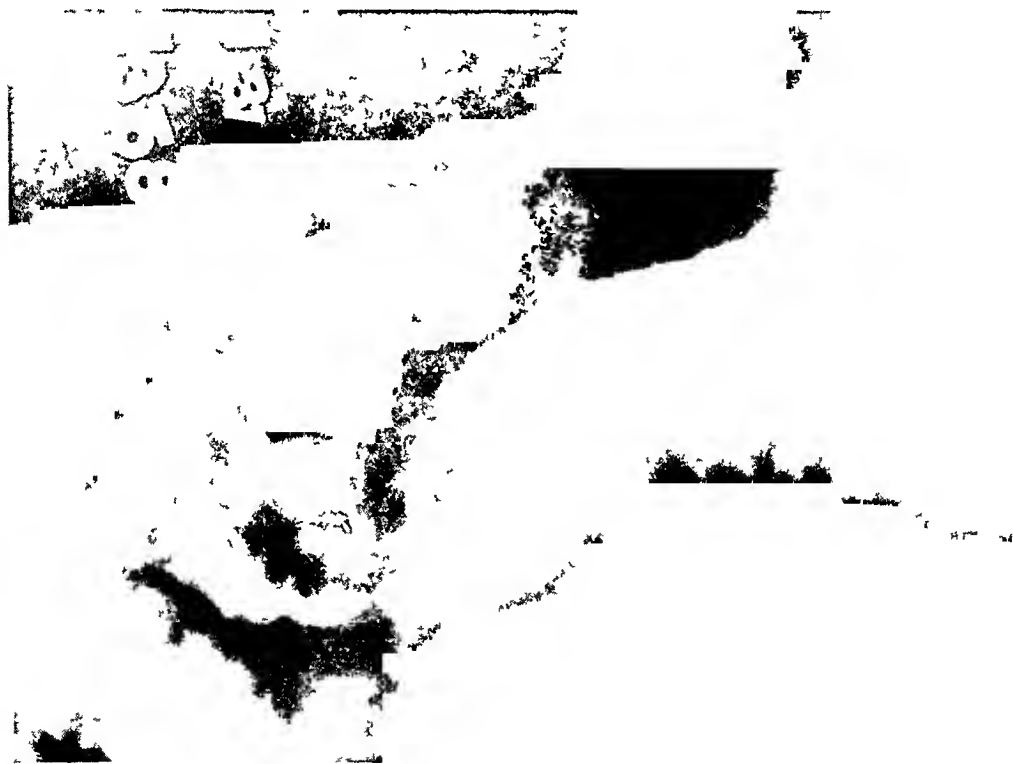


FIG 2 Large central niche appearing on pressure

Differences in bases of computation may also account for some of the variances. All estimates from the clinic, including those of Carman and Sutherland (13.27 per cent of niches), those of Kirklin (15.24 per cent), and the present computation of 17.7 per cent, represent the ratio of cases in which a niche was discerned to the total number of cases in which duodenal ulcer was diagnosed roentgenologically. It is true that by no means all of these diagnoses had been confirmed surgically or otherwise, for the larger proportion of the patients were not operated on, and in a great number of cases the ulcers undoubtedly were healed at the time of examination. But,

at this clinic, errors in the roentgenologic diagnosis in cases in which patients were operated on have not for many years exceeded 5 per cent, hence it was considered fair and reasonable to take the entire number of diagnoses as a basis for calculating the percentage of niches seen with roentgen-rays. Further, the patients were not a selected group with such marked gastroduodenal symptoms that positive roentgenologic data could be expected, but many patients were included whose symptoms were vague, trivial or ancient and for whom the examination was ordered as a routine to exclude organic disease of the digestive tract. Thus it is safe to assume that healed

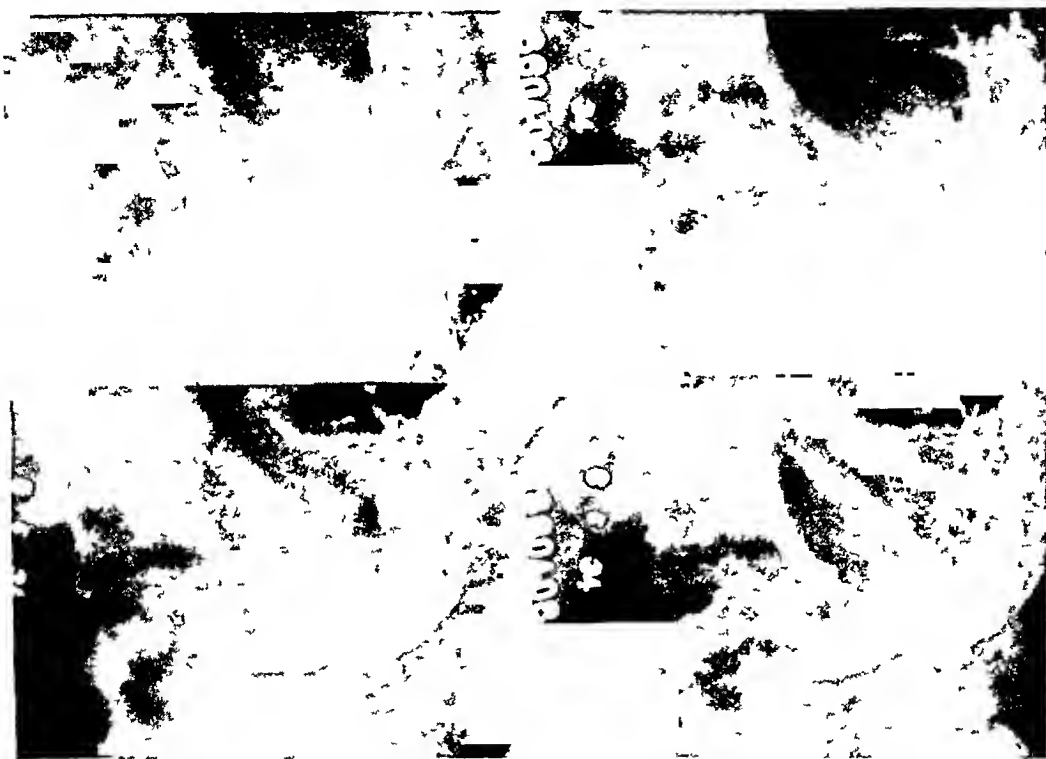


FIG 3 Central niche, constant in all four views

ulcers predominated over those that were active and that ulcers with craters were decidedly in the minority.

Akerlund's estimate, in 1931, of 75 per cent of niches was based on "cases of ulcer definitely established radiologically," Geyman's 64 per cent on "bulbs having deformity characteristic of duodenal ulcer," and Clark and Geyman's 54 per cent on "all cases of duodenal ulcer." In contrast with these, Berg's 50 per cent was based on "all cases proved by operation," and Diamond's statements indicate that his 66.6 per cent was also derived from surgically proved cases. Ordinarily, patients having duodenal ulcer are not subjected to operation unless symptoms and signs are severe, and such patients are likely to have a relatively high ratio of active ulcers with

craters capable of demonstration as niches. It is noteworthy, however, that equally high or higher percentages of niches were found by some of the observers in patients in whom roentgenologic evidence of an ulcer was conclusive but many of whom presumably were not operated on. But this apparent inconsistency should not be overemphasized, for the basic groups that included nonsurgical cases may have comprised chiefly patients who had pronounced symptoms and hence probably had a large proportion of active, crateriform ulcers. As an instance in point, we reviewed the first 100 cases of clinically active duodenal ulcer encountered in the roentgeno-

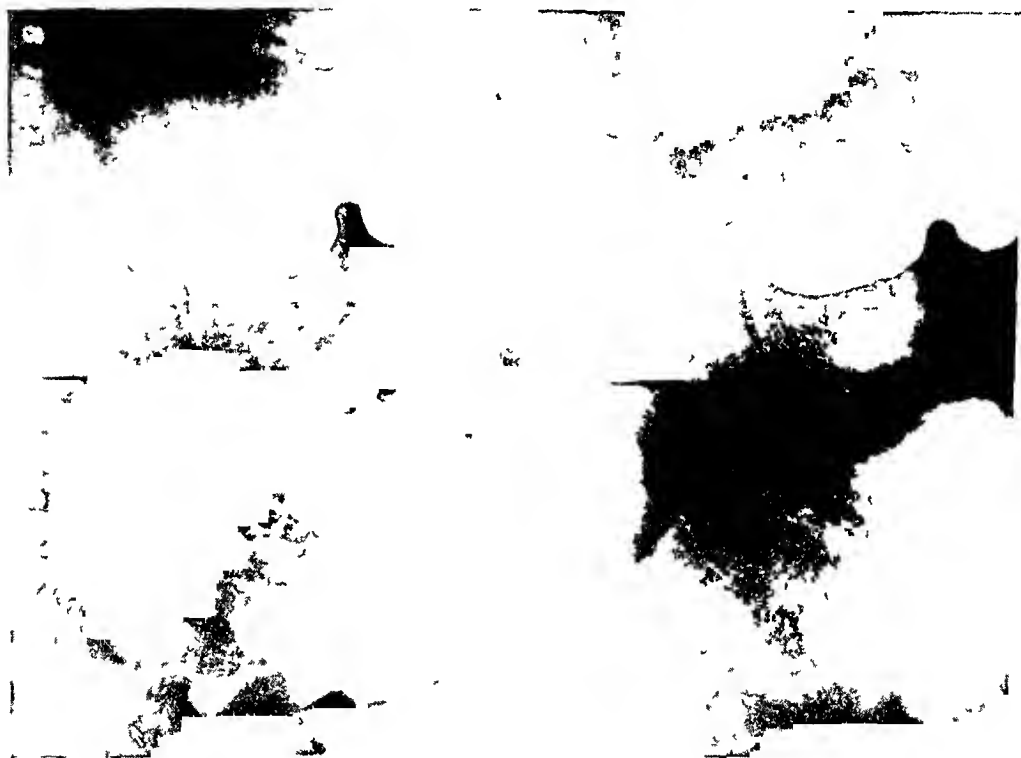


FIG 4 Large niche in second portion of duodenum

logic section of the clinic this year. In each of these cases the syndrome, with or without signs of hemorrhage, was so emphatic at the time of examination that the clinician regarded the lesion as active, and a roentgenologic niche was discerned in 38 of the 100 cases. In other words, the incidence of crateriform ulcers in this selected group of cases is twice as high as in the unselected group.

To obtain anatomic data on the incidence of the niche, we have studied 176 ulcers taken at necropsy from 140 subjects during the period from January 1, 1931 to January 1, 1934. Among the 140 subjects, 67 had healed ulcers only, 14 had both healed and active ulcers, and 59 had active ulcers only. In 66 of these 67 cases of healed ulcers alone no pit remained

at the site of the lesion, in only one was there a minute depression which might have been construed as a niche at roentgenologic examination. Of the 73 cases in which ulcers had been active (14 plus 59) there were definite craters in thirty-six. Thus craters probably demonstrable as roentgenologic niches during life were present in 37 of 140 subjects, or 25.4 per cent. Of the 73 with active ulcers, if this group is taken as a basis, slightly less than 50 per cent had ulcer craters that were potentially demonstrable as niches. On the other hand, of the 176 ulcers, comprising healed, active, combined, and multiple lesions, only 40, or 22.7 per cent, were capable of exhibition as roentgenologic niches.

This low anatomic incidence is consonant with the still lower roentgenologic incidence observed at the clinic, for the roentgenologist cannot discover all existing craters. Our data are not presented as being decisive. It could be argued that an apparently craterless ulcer in a cadaver might have produced a demonstrable roentgenologic niche during life, when the tissues were engorged and the contractile tonus of the muscularis mucosa was present. It could also be argued that subjective elements entered into judgment as to the presence or absence of a crater, although every effort was made to avoid prejudice and to resolve doubts in favor of the presence of a niche. In fact, conclusive statistics as to the frequency with which niches occur can scarcely be obtained, for in every case it would be necessary to show that the roentgenologic niche corresponded precisely to a crater disclosed at operation or at necropsy, and even here the personal equation would enter. So, although for the reasons cited we adhere to the belief that the actual incidence of the niche in material comparable to ours is low, we do not question the skill or competence of observers who report high percentages. Indeed, we would be glad if we could confirm their opinion, for the niche is an important item in the diagnosis of ulcer.

SIGNIFICANCE OF THE NICHE

Roentgenologically, the niche has a threefold significance, for it is an important sign of ulcer, indicates that the ulcer is active, and is a valuable criterion in appraising the effect of treatment.

A definite niche is pathognomonic of ulcer, and the only sign that is pathognomonic. Occasionally a niche is the sole sign, and in all other respects the duodenum is normal (figure 5). Usually, in such cases, the niche appears as a comparatively dense fleck internal to the bulbar contour when the duodenal walls are approximated by compression. Further, when the bulb presents multiple sacculations, it is seldom safe to assume that any particular recess is the crater of an ulcer unless a corresponding internal or marginal fleck persists under manipulation, and an incisure opposite a marginal recess is much less convincing evidence that the recess is the crater of an ulcer. Another rare and striking variety of niche is the accessory pocket produced by a perforated ulcer with excavation into the pancreas or

liver. The more or less rounded cavity fills with barium and the narrow channel leading to the duodenum is usually depicted. These tributes to the niche do not detract from the general reliability of duodenal deformity as a sign of ulcer. Simulants from other causes are well known and can usually be identified, and if reliance could not be placed on deformity, a large proportion of ulcers would escape recognition. The only shortcoming of this sign is that by deformity alone active ulcers cannot be distinguished from those that are healed.

The niche is practically an unequivocal sign that an ulcer is active, for

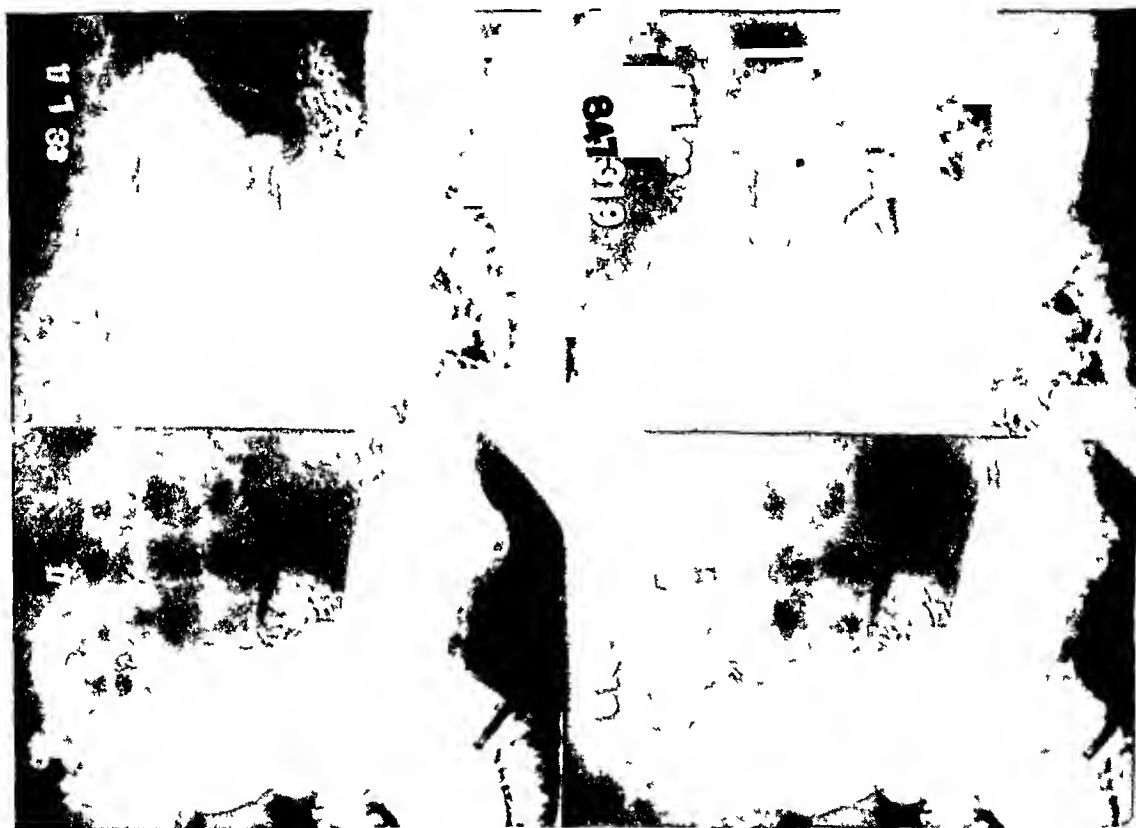


FIG 5 Large central niche depicted in two lower views under pressure, in the two upper views, made without pressure, the bulb appears to be normal

healed ulcers with demonstrable depressions are so rare that they can be disregarded. But the niche is not the sole sign of activity. Increased irritability of the bulb, as shown by rapid emptying and quickly changing contour, is an equally trustworthy index. Often, in addition, the internal relief has the diffusely mottled appearance characteristic of duodenitis, and the activity of the process cannot be doubted. When the bulb is deformed, but a niche cannot be discerned and marked irritability or evidence of duodenitis is also absent, it is the custom at the clinic to return a roentgenologic

diagnosis of ulcer and leave to the clinician the task of determining whether it is probably active or healed

In determining the response of an ulcer to treatment, the niche is a factor of moment. If the niche diminishes or vanishes, it is indicative of progress toward cure. But disappearance of the roentgenologic niche does not necessarily signify that the ulcer has healed. Roentgenologists agree that florid ulcers often have no discernible craters. Mann has shown that the craters of experimentally produced peptic ulcers in process of healing gradually fill with granulation tissue, and that by proliferation of the marginal mucosa the granulation tissue is forced out of the crater like a plug. These observations accord with the cited ratio of craters in active ulcers found at necropsy and support the opinion that in the usual series of patients having healed, partially healed, and florid ulcers, niches would scarcely be demonstrable in more than 25 per cent of cases.

Whatever its incidence may be, the niche should be sought for diligently at every examination, for it is incumbent on the roentgenologist not only to discover existing ulcers, but also to furnish all available information concerning their activity.

BIBLIOGRAPHY

- AKERLUND, A. Roentgen diagnosis of ulcer duodeni with respect to the local "direct" roentgen symptoms, *Acta Radiol*, 1923, II, 14-30
- AKERLUND, A. Present-day criteria of x-ray diagnosis of duodenal ulcer, *Am Jr Surg*, 1931, XI, 233, 504
- ALBRECHT, H. U. Quoted by Geyman
- BERG, H. H. Direct signs of duodenal ulcer, *Brit Jr Radiol*, 1925, XXV, 372-376
- CARMAN, R. D., and SUTHERLAND, C. G. Duodenal niche, *Am Jr Roentgenol and Radium Therap*, 1926, XVI, 101-106
- CLARK, D. M., and GEYMAN, M. J. Roentgen evidence of healing in duodenal ulcer, *Jr Am Med Assoc*, 1934, CII, 107-112
- COLE, L. G. The diagnosis of post-pyloric (duodenal) ulcer by means of serial radiography, *Lancet*, 1914, I, 1239-1244
- DIAMOND, J. S. Niche as roentgen sign of duodenal ulcer with a report of 42 cases, *Radiology*, 1925, IV, 93-100
- ETTINGER, A., and DAVIS, W. E. X-ray diagnosis of activity and cure of duodenal ulcer, *Am Jr Digest Dis and Nutrition*, 1934, I, 579-581
- GEYMAN, M. J. Evaluation of compression technique in roentgen demonstration of duodenal lesions, *Am Jr Roentgenol and Radium Therap*, 1932, XXVIII, 211-222
- HAUDER, M. Der radiologische Nachweis des Ulcus duodeni, *Med Kln*, 1912, VIII, 181-224
- KIRKLIN, B. R. Duodenal ulcers that may escape roentgenologic diagnosis, *Med Clin N Am*, 1931, XV, 177-184
- MAHON, F. C. Chemical and mechanical factors in experimentally produced peptic ulcer, *Surg Clin N Am*, 1925, V, 753-775

PERSONALITY AND THE ENDOCRINES, A STUDY BASED UPON 1400 QUANTITATIVE NECROPSIES³

By WALTER FRELMAN, M D , F A C P , *Washington, D C*

In recent times there has been intensive study of the excesses and deficiencies of the glands supplying hormones to the body, and a multitude of clinical syndromes have been described. It is now possible, on the basis of structural and biochemical studies, to identify disturbances in a number of these glands. When it comes to personality studies in relationship with the endocrine system, however, there is a school of thought which, in the words of Benjamin Franklin¹ concerning the medical school in Edinburgh, "seems better calculated to please the fancy than to form the Judgment". The Italian school of constitutional pathologists under Viola² probably started this trend of thought, but, like many another imported plague, the idea became pandemic, and reached its acme in Berman's book, "The Glands Regulating Personality"³. At the present time the antiviral of common sense, aided by truly scientific researches, has brought about a better balance, so that Hoskins⁴ can write "To those who, in the present state of our knowledge, would glibly re-write physiology and psychology in terms of pituitary functions the timorousness of the proverbial angel is commended".

THE PERSONALITIES

In previous communications presented before this College^{5, 6} four fundamental personality reaction types have been described: cycloid, paranoid, schizoid and epileptoid. The individual of cycloid temperament is extraverted, industrious, subject to fluctuations in mood, athletic and highly sexed. The paranoid individual is reserved, suspicious, antagonistic, embittered and calculating. The schizoid patient is introverted, retiring, self-deprecatory, studious, meticulous and low in physical vitality. The epileptoid individual is moody, pedantic, devout, and subject to paroxysmal headaches, rages, fits. When any person suffers a sufficient exaggeration of one of these trends (which may be found in all people) he becomes dangerous to himself or others and requires psychiatric care. It has further been emphasized in the previous studies that these underlying personality reactions may become exaggerated not only as the result of some as yet obscure etiology resulting in the so-called major psychoses, but also as the result of organic disease of the brain such as senility, syphilis, arteriosclerosis, and the like. When the controlling balance of the mind breaks down, the in-

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935

From Blackburn Laboratory, St. Elizabeth's Hospital, and the Department of Neurology, George Washington University, Washington, D C

dividual's personality deviates more or less in one or another of the directions enumerated above, cycloid, paranoid, schizoid, or epileptoid. This is the reason why material from psychotic patients offers such a splendid opportunity for the investigation of various somatic factors involved in the genesis and determination of the personality of the individual. If it can be shown, for instance, that those who show a paranoid trend have large suprarenal glands and small thyroids, some insight may be gained into the mechanism of personality. A biometrical study⁷ that will shed light on this question is now under way. In a recent paper dealing with the weight of the endocrine glands,⁸ I concluded with the apologia: "In defense of this method of approach to the study of mental disorders, it may be said that if statistically significant differences are found in the glands of men who behave differently, even though due allowances are made for age, sex, race, weight, and stature, then these differences will assume an importance far beyond the few grams, or milligrams even, that may separate their mean weights."

THE MATERIAL

During the past 10 years, psychotic patients dying at St. Elizabeth's Hospital have been submitted to quantitative necropsy, even the pineal and parathyroids being removed and weighed before being studied histologically. Moreover, in most of the cases it has been possible to obtain photographs of the body beforehand so that growth disorders and constitutional types might be determined. The material has been classified into the four personality types irrespective of the etiology of the mental disorder by my colleague, Dr. Nolan D. C. Lewis.

For the purpose of this study I have selected from the material cases showing the most marked deviations in the weight of the individual endocrine glands with the possibility in mind that there might be a general family resemblance, so to speak, among those possessing, say, large normal thyroids, which might be contrasted with the characteristics of a group showing small thyroids.

The dangers of too implicit reliance upon postmortem data cannot be too frequently reiterated. Nevertheless, until the time comes when clinical assay of active endocrine principles in the circulating blood becomes possible, the method of pathologic anatomy must receive due consideration. Too many patients with outspoken diabetes have been found to possess an abundance of normal islet tissue, and too many patients with sclerosis and hyalinization of the islets of Langerhans have been innocent of glycosuria to make it axiomatic that diabetes mellitus is a disease only of the pancreas. In all probability there are large factors of safety in each endocrine organ and also, as has been abundantly proved, interrelationships among the glands that balance one against the other.

The biometrical method is empirical. Let us examine the results

LARGE GLANDS AND SMALL GLANDS *

Epiphysis The pineal gland averages between 150 and 185 mg in weight. Twenty-six patients, with glands weighing 400 mg or over, were compared with 24 patients carrying glands weighing less than 50 mg. No differences whatever could be observed in the trend of the personality.

Hypophysis The important sex differences in the pituitary gland make it advisable to consider males and females separately. In the male the gland averages from 690 to 730 mg in weight. Twenty men with pituitaries weighing over 1000 mg were compared with 14 men in whom the pituitary weighed 400 mg or less. The material is small but the proportionate representation of each of the personality reaction types is almost exactly that of the whole group of 1400 cases. In the female, the average weight of the gland is from 760 to 815 mg. Fifteen women, with glands weighing 1100 mg or more, were compared with 21 possessing glands weighing 500 mg or less. From the standpoint of personality there is a little higher incidence of manic-depressive temperament (cycloid personality) in those possessing large pituitaries, while an unusually large percentage (4 out of 21 cases) of those with small hypophyses were undifferentiated as to personality. From this it may be inferred that the pituitary supplies an energy drive that enables the personality to unfold. There is little evidence that it determines the personality, since the great groups of schizoid and paranoid personalities are almost perfectly balanced.

Thyroid The weight of the normal thyroid gland ranges, on the average, between 16 and 23 grams. Fifteen patients, with healthy thyroids weighing 50 grams or more, were compared with 21 patients in whom the gland weighed less than 8 grams. The material is quite small, but again there is an undue proportion of patients with undifferentiated personalities among the "small-thyroid" group, and a correspondingly large representation of the cycloid group in those bearing large thyroids. It is quite striking that 10 of the 22 "small-thyroid" patients had pituitaries weighing 500 mg or less.

In view of the relationship emphasized by Hoskins between thyroid deficiency and dementia precox with its predominant schizoid tendency, special attention was given to the presence of small thyroids in association with schizoid personalities. In the females, this association was quite suggestive, but in the males the opposite trend was observed. It seems likely that the driving force of the thyroid is of importance in developing the personality rather than in orienting it in any particular direction.

Parathyroids The parathyroid glands average from 145 to 170 mg in weight. Thirty-one patients, with glands weighing 300 mg or more, were compared with 21 patients with glands weighing 50 mg or less. In

* The averages given are those obtained in the previous study⁸ the two figures representing the upper and lower figures for sex-race combinations. For instance in the case of the pineal the figures are white male, 172 mg, colored male, 151 mg, white female, 183 mg, colored female, 157 mg.

view of the suspected relationship between hypoparathyroidism, tetany and epilepsy, it was illuminating to find two epileptics with large parathyroids, and one with small parathyroids. Furthermore, with regard to the known irritability of the nervous system in parathyroid deficiency, it was unexpected to find the aggressive paranoids and submissive schizoids exactly balanced. There was a moderate percentage of cycloid individuals with large parathyroids, while this temperament was disclosed only once among those having unusually small parathyroids. On the whole, it must be concluded that the parathyroids are of little importance in the fundamental personality trend of the individual.

Thymus The thymus averages from 12 to 18 grams in weight. It is extremely susceptible to changes in nutrition so that the weight of the gland is of relatively little importance. On the other hand, there is ordinarily an involution of the parenchymatous elements, so that in this gland the percentage of lymphoid tissue has been correlated with personality type. Thirty-two patients with thymus glands presenting 20 per cent or more of parenchymatous tissue were compared with 42 patients in whom the thymus tissue was reduced at most to a few strands. The outstanding feature was the high proportion (44 per cent) of epileptoid personalities in the persistent thymus group, whereas in the whole number of cases, the epileptoids account for only 8.6 per cent. There were three epileptoids among the 42 cases with completely involuted thymuses. Does this mean that the thymus determines the epileptoid personality reaction? There appears to be some disturbance of the general bodily development in a fairly large number of those presenting persistent thymus glands, a softness and rounding of contours indicating possibly a positive water balance. On the other hand, the thymus is known to undergo rapid involution in response to various unfavorable conditions like infections and especially wasting diseases. Most of the epileptoids die rather rapidly when their time arrives, and as a group they are younger, so that while the association of persistent thymus and the epileptoid reaction is a pronounced one, it would be hazardous to state that epilepsy is due to persistence of the thymus gland. In any case, it should be an easy matter to provoke involution in the thymus by means of roentgen-rays in a large number of epileptics and to study the results. The schizoid and paranoid personality reactions show no differences, while individuals with cyclothymic tendencies have a little higher representation in the "small-thymus" group.

Suprarenals The suprarenal glands average from 12.5 to 15.5 grams in weight. Twenty-three patients with glands weighing 20 grams or more have been compared with 25 others carrying glands weighing less than 8 grams. Lack of personality differentiation is again a feature of those with small suprarenal glands, six out of the 25 presenting insufficient personality characteristics to allow them to be grouped. On the other hand, among those with large suprarenals there is a slightly greater representation

of the aggressive paranoid group The differences are too small, however, to be more than suggestive

Testes • The weight of the testes averages from 25 to 30 grams In this study 31 patients with testes weighing over 45 grams were compared with 18 patients in whom the testes weighed less than 10 grams Nine of the 31 with large testes belonged in the cycloid group, while only one patient with small testes fell in the same group As shown in a previous communication,⁹ the large testis seems to be a rather general characteristic of the cycloid group Except for this, there is no outstanding difference between the large-testis group and the small-testis group although paranoid personalities are common in the latter The histories of these patients have not been exhaustively studied, but it is mentioned in the abstracts of three of the former that homosexuality was present, while this phenomenon was not encountered among those possessing small glands

In contrast with the mildly suggestive findings on correlating the size of the testes with the type of personality, it seems justifiable to point to the rather pronounced somatic differences observed in these two groups, as indicated in the accompanying table

TABLE I

Incidence of Somatic Disorders and Personality Deviations Correlated with Size of Testes

	Percentages										Personality				
	Number	Per cent	Blood pressure over 160 mm	Circulatory deaths	Hirsutism	Bald crown	Large hips	Gynecomastia	Hairless body	Homosexuality	Personality undifferentiated	Cycloid personality	Paranoid personality	Schizoid personality	Epileptoid personality
Large testes	31	100	55	45	31	58	36	0	22	10	7	29	32	29	3
Small testes	18	100	54	5	0	11	61	17	83	0	12	6	55	22	5

Ovaries The ovaries average four to five grams in weight A group of 15 women whose normal ovaries weighed more than 10 grams was compared with another group of 27 women whose ovaries weighed less than 17 grams Aside from a comparatively low incidence of paranoid individuals among those possessing large ovaries, no outstanding deviations from the normal distribution were noted

DISCUSSION

The relatively slight relationship between the condition of the individual endocrine glands and the fundamental personality of the individual possessing them has been emphasized by Curschmann¹⁰ as follows "In spite of

marked psychic sluggishness the premorbid psychic personality is always and even strongly preserved in severe myxedema" Furthermore, Engelbach¹¹ states "One of the most common reactions attributable to the nervous system (in endocrine diseases) is that of general exhaustion and incapacity, which can be related to nearly all of the ductless glands" Finally forecasting the results of this endocrine study I¹² stated "The study of the constitution will reveal the slight part played by the endocrine glands as such (with the exception of the thyroid) in the development and direction of the psychoses, and the dominant position of these glands in the ordering of bodily growth and form"

What may be said on the other side? Wertham¹³ in a constitutional study of 923 cases of mental disease, found 21 per cent in whom disorders of growth were present in one form or another The incidence was highest (36 per cent) among the schizophrenics, about equal in the paranoids and epileptoids (29 and 26 per cent) and lowest among the manic-depressives (2 per cent) Following these observations he states "Just as patients with manic-depressive psychoses show a tendency toward unstunted and harmonious bodily growth so they are also usually personalities with likewise harmonious mental maturation The affective psychosis interrupts this mental development, but in most cases does not essentially deflect it Schizophrenic patients, on the other hand, who show the largest number of disorders of physical growth, frequently show also in their prepsychotic mental development traits of inharmonious growth, immaturity and combinations of mental precocity and arrested development in intellectual, emotional and instinctive life"

Notkin¹⁴ surveyed the population of a state hospital and found only eight cases of outright endocrinopathy among 6000 patients "This infrequency seems to indicate that the relationship of the endocrine dysfunction to mental disorders has been overrated considerably, especially if we bear in mind the frequent occurrence of endocrine dysfunction without psychoses"

Experiments upon animals, and operations upon human beings serve to corroborate the conclusions to be drawn from the study of the material presented in this paper Castration in either male or female does not alter the fundamental personality of the individual, turn him from a cycloid temperament to a schizoid one or vice versa Nor does excision of the thyroid gland nor destruction of the hypophysis by disease The patient with Addison's disease may present certain peculiarities of behavior that stamp him as different from his fellows, but given even as small a number as 20 patients with Addison's disease it is fairly certain that all the personality types enumerated above will be found among them

The question of personality lies deeper in the mists of genetic constitution than in the endocrine system

Two important functions, as far as the personality is concerned, may safely be granted to the endocrine system These are emotional stability,

and energy drive. The irritability and emotional instability seen in hyperthyroidism, in hyperinsulinism, in hypoparathyroidism and in certain other endocrinopathies, are relieved by restoring the normal endocrine balance. The energy drive is augmented to a greater or less degree by correcting any deficiency of the hypophysis, thyroid, suprarenals or gonads. Nevertheless, as far as determining whether an individual shall be a proud, sensitive, suspicious, paranoid individual or a timid, shut-in dreamy schizoid person, a boisterous, jolly, hail-fellow-well-met cycloid, or a moody, pedantic, egocentric epileptoid individual, the endocrine glands would seem to have little say in the matter.

REFERENCES

- 1 PEPPER, W. The medical side of Benjamin Franklin, 1911, W. J. Campbell, Philadelphia, p. 53.
- 2 PENDE, N. Constitutional inadequacies (translated by S. Naccarati), 1928, Lea and Febiger, Philadelphia.
- 3 BERMAN. The glands regulating personality, 1921, Macmillan Co., New York.
- 4 HOSKINS, R. G. The tides of life, 1933, W. W. Norton and Co., New York.
- 5 FREEMAN, W. Psychological panel in diagnosis and prognosis, *ANN INT MED*, 1930, iv, 29-38.
- 6 FREEMAN, W. Human constitution, *ANN INT MED*, 1934, vii, 805-811.
- 7 PEARL, R., GOOCH, M., and FREEMAN, W. A biometric study of the endocrine organs in relation to mental disease, *Human Biol*, 1935 (Sept. and Dec.).
- 8 FREEMAN, W. Weight of endocrine glands, *Human Biol*, 1934, vi, 489-523.
- 9 FREEMAN, W. Organic constitution of the cyclothymic, U. S. Dept. of Interior, St. Eliz. Hosp., Bull. No. 7, 1931, 60-69.
- 10 CURSCHMANN, H. Die Hypothyreosen der Erwachsenen, in HIRSCH, M. Handb. d. inn. Sekretionen, 1928, Kabitsch, Leipzig, iii, 79.
- 11 ENGELBACH, W. Endocrine medicine, 1928, Charles C. Thomas, Baltimore, i, 434.
- 12 FREEMAN, W. Human constitution, in BENTLEY and COWDRY. The problem of mental disorder, 1934, McGraw-Hill, New York, 227-233.
- 13 WERTHAM, F. I. Incidence of growth disorders in 923 cases of mental disease, *Arch. Neurol. and Psychiat*, 1929, xxi, 1128-1140.
- 14 NOTKIN, J. Clinical study of psychoses associated with various types of endocrinopathy, *Am. Jr. Psychiat*, 1932, xii, 331-346.

THE RELATIONSHIP OF THE FLAT CHEST TO INTELLIGENCE

By S A WEISMAN, M D , F A C P , *Minneapolis, Minnesota*

IN a series of reports ¹ previously published I emphasized the following facts

- 1 That the healthy normal adult chest was, contrary to the general belief, flat and that the tuberculous chest was deep
- 2 That at birth the chest is almost round, and that by the age of five about 87 per cent of the total flattening out process already has taken place, and that there is only about 13 per cent difference between the contour of the chest of a five year old child and a fully mature adult type of chest, which is attained at puberty
- 3 That children from better environmental districts are not only taller and heavier but also have a flatter type of chest

It is the purpose of this study to determine whether or not there is any correlation between the shape of the chest and intelligence

In 1893, Porter,² from a study made on many thousands of St Louis school children concluded, "Children who possess more than ordinary power of mental labor, as measured by their progress in their studies, are heavier, taller and larger in girth of chest than their less gifted companions of the same age"

About thirty years ago Rietz's³ measurements of the height and weight of some 20,000 Berlin school children showed that brighter children are better developed physically

Goddard's⁴ measurements of the height and weight of feeble minded children indicated that there is a close correlation between physical growth and mental activity, and in 1917 Courtis⁵ believed that children who are poorly developed physically are usually dull mentally

Francis Galton,⁶ in his book "Hereditary Genius," published in 1869, concluded that men of genius tend to be well developed physically He states, "A collection of living magnates in various branches of intellectual achievement is always a feast to my eyes being, as they are, such massive, vigorous, capable-looking animals"

In 1918 Gowin⁷ made a study of the height and weight of 1,037 American executives, which number included governors, United States senators, mayors of leading cities, University presidents, bishops, merchants, manufacturers, insurance company presidents, and railroad company presidents He found the average height to be 71 4 inches and the average weight 181 1 pounds (table 1) The average height of 1,000,000 United States army recruits is 67 5 inches

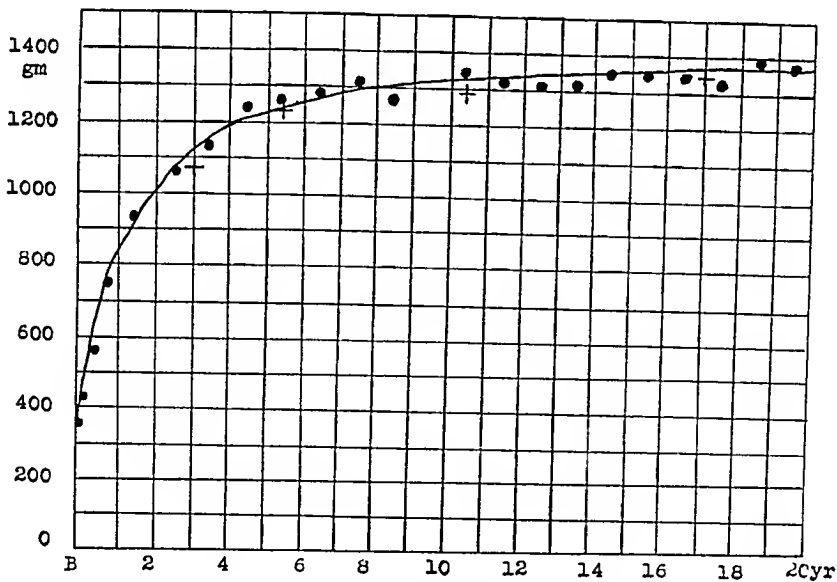
* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935
From the Department of Medicine, University of Minnesota and Glen Lake Sanatorium, Oak Terrace, Minnesota

TABLE I
Physique in Relation to Position
(Gowin)

Class	Height	Difference	Weight	Difference
Bishops	5 10 6		176 4	
Preachers, Small Towns	5 8 8	1 8 in	159 4	17 0 lb
University Presidents	5 10 8		181 6	
Presidents, Small Colleges	5 9 6	1 2 in	164 0	17 6 lb
City School Superintendents	5 10 4		178 6	
Principals, Small Towns	5 9 7	7 in	157 6	21 0 lb
Presidents, State Bar	5 10 5		171 5	
County Attorneys	5 10 0	5 in	162 4	9 1 lb
Sales Managers	5 10 1		182 8	
Salesmen	5 9 1	1 1 in	157 0	25 8 lb
Railroad Presidents	5 10 9		186 3	
Station Agents	5 9 4	1 5 in	154 0	31 7 lb

Woodrow ⁸ in 1919 and Baldwin and Stecher ⁹ in 1922 showed that there is an intimate relationship between mental and physical development

In the development of the brain Scammon ¹⁰ has shown that the greatest percentage of growth takes place in the first year of life and that by the age of five the brain has attained to about 85 per cent of its total adult weight (graph 1) This development of brain weight runs practically parallel with the flattening out process of the chest from infancy to maturity



GRAPH 1 Observed and calculated weight of the total brain (both sexes)—from birth to twenty years (Scammon)

TABLE II

Relationship of Scholastic Standing to Thoracic Index—Girls

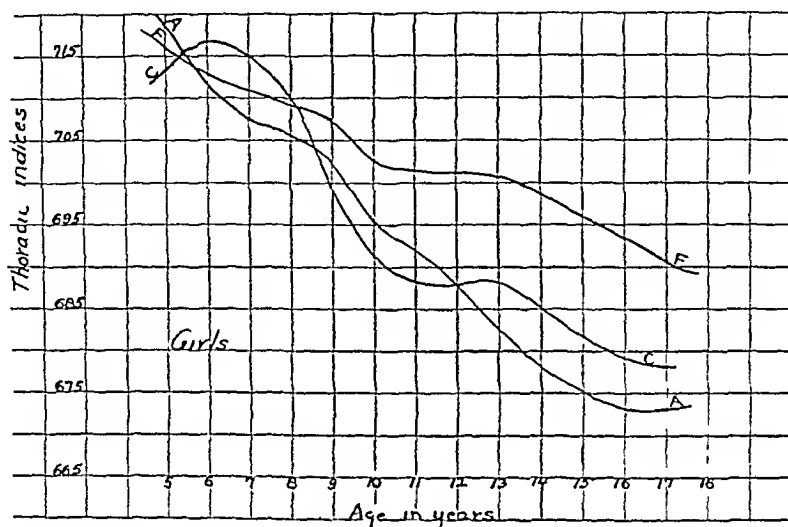
Age	Grade	No Cases	Av T I	Av Dev	St Dev	P E
5	F	35	721	3 8	4 01	4586
	A	29	725	3 6	4 22	5261
	C	199	714	3 4	4 70	1488
6	F	129	710	3 4	4 27	2495
	A	106	706	3 2	4 44	2900
	C	444	713	3 1	4 12	1281
7	F	111	705	3 4	3 05	1888
	A	90	706	3 6	4 46	3102
	C	475	723	3 8	4 68	1484
8	F	111	717	3 4	4 09	2563
	A	127	708	2 9	3 84	2225
	C	595	709	3 2	4 23	1147
9	F	127	704	3 7	4 17	2495
	A	77	703	3 8	4 82	3710
	C	671	702	3 2	4 30	1147
10	F	131	699	1 9	4 19	2361
	A	84	698	3 2	3 90	2832
	C	610	695	3 6	4 60	1281
11	F	139	701	3 5	4 22	2361
	A	65	684	4 2	5 39	4519
	C	371	676	2 8	4 25	1416
12	F	111	707	3 8	4 83	2833
	A	30	686	3 1	3 97	4845
	C	537	696	3 9	4 82	1349
13	F	57	695	4	5 20	4656
	A	45	698	4 5	6 11	6137
	C	331	690	4 3	5 31	2225
14	F	62	702	4 2	5 70	4858
	A	44	688	3 6	4 70	4719
	C	308	683	4 5	5 43	2090
15	F	74	690	4 2	5 32	4114
	A	18	652	2 3	2 69	4384
	C	358	681	4 2	5 48	2023
16	F	41	706	5 6	6 70	6745
	A	11	679	5 5	8 53	1754
	C	208	679	4 2	4 95	2292
17	F	27	682	4 3	5 19	6699
	A	7	675	4 0	4 66	1 214
	C	83	677	4 5	5 03	3709
18	F	7	733	3 1	4 18	1 079
	A	2	654	2	2 24	1 011
	C	17	691	5	5 99	9438

TABLE III
Relationship of Scholastic Standing to Thoracic Index—Boys

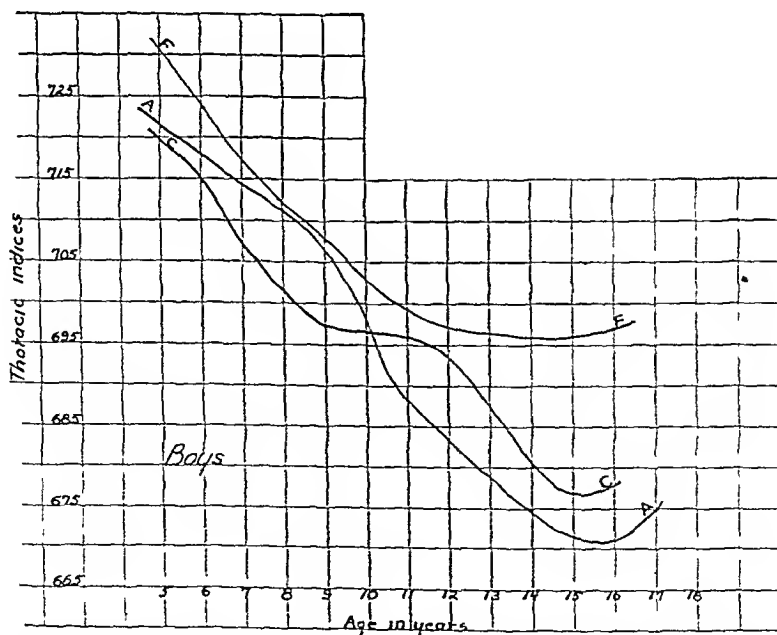
Age	Grade	No Cases	Av T I	Av Dev	St Dev	P E
5	F	37	735	3	3 5	3794
	A	21	728	4 2	5 1	7486
	C	186	724	3 5	4 4	2158
6	F	175	724	3 6	5 1	261
	A	67	710	4	5	404
	C	473	712	3 4	4 2	128
7	F	225	715	3 3	2 4	1074
	A	49	712	3 1	4 1	3913
	C	438	710	3 2	4	1281
8	F	275	713	3 3	4 24	1753
	A	68	715	3	3 6	2986
	C	593	702	3 1	3 6	0944
9	F	214	709	3 5	4 3	202
	A	47	717	3 8	4 6	45
	C	605	697	3 2	4 29	1146
10	F	234	704	3 3	4 42	1966
	A	50	692	3 2	4 08	3842
	C	677	693	3 2	4	1011
11	F	209	696	3 3	4 22	1956
	A	42	686	3 5	4 6	4113
	C	570	699	3 7	4 6	0539
12	F	164	696	3 2	4 6	2495
	A	23	683	4	5 25	5193
	C	417	698	3 6	4 43	1417
13	F	158	699	4 1	5 23	2757
	A	25	689	4	6 1	8094
	C	226	689	3 8	4 5	2023
14	F	101	691	4 6	3 5	2293
	A	13	673	2 1	3 1	5598
	C	291	679	3 9	3 8	2225
15	F	170	702	4 5	5 48	2842
	A	17	666	2 2	4 4	6745
	C	297	675	4 3	5 4	2090
16	F	137	694	4 2	5 1	3102
	A	9	665	2 5	2 9	6745
	C	237	671	4 2	5 49	2428
17	F	53	691	5 4	6 7	6070
	A	6	684	5	5 7	1 551
	C	110	687	4 4	5 4	3439
18	F	10	718	5 2	6 1	1 281
	A	2	669	2	1 4	9510
	C	28	685	5 4	4 9	5600

Therefore, the deduction occurred to me if, as shown by the aforementioned investigators, taller and heavier individuals tend to be more intelligent, and, as shown by my previous studies, taller and heavier children have the flatter, more healthy type of chest, then there should be a correlation between the flat chest and intelligence

The present study was made on 14,844 Minneapolis school children, from



GRAPH 2 Relationship of thoracic index to scholastic standings These curves represent the average thoracic indices with one application of the three point rule



GRAPH 3 Relationship of thoracic index to scholastic standings These curves represent the average thoracic indices with one application of the three point rule

the ages of five to seventeen. This number consisted of 7,740 boys and 7,104 girls. The school grades, as given by the teachers, were considered a measure of the child's intelligence. The grades were divided into three groups. The "A" students were put into the class "A" group, the "B" and "C" students were put into the class "C" group, and those below, including the subnormals, were put into the "F" group.

The average thoracic index was then determined for each group according to age (tables 2 and 3, graphs 2 and 3). The thoracic index is the ratio of the depth of the chest to the width, taken against the skin at the nipple line.

The findings indicate that the "F" group have, on the average, a deeper chest, that is, a higher thoracic index than the "A" and "C" groups. This difference seems to be much more marked just before the age of nine in the girls and perhaps a little later in the boys. From there the difference between the "A" group and the "F" group becomes markedly greater. The "C" group seems to fall in between the "A" and the "F" groups after the age of 12 in the girls and between the ages of 10 and 11 for the boys. Before these ages the "C" boys seem to have the flattest type of chest, and the girls' "C" group is flatter than the "A" group between the ages of nine and almost twelve. After age 12 in the girls and ten and one-half in the boys the "A" group, both in the boys and in the girls, shows a definitely flatter type of chest, or one with a lower thoracic index.

CONCLUSIONS

1 The flat-chested children are taller and heavier than the deep-chested children.

2 There appears to be a definite correlation between the shape of the chest and intelligence in children.

3 The flat chested children have, on the average, better school grades.

4 Therefore, it is evident that the flat chested children are, on the average, taller, heavier, and display a higher degree of intelligence.

BIBLIOGRAPHY

- 1 WEISMAN, S. A. Contour of normal and tuberculous chests, *Jr Am Med Assoc*, 1927, LXXXIX, 281-284.
- WEISMAN, S. A. Further observations on the contour of normal and tuberculous chests, *Arch Int Med*, 1929, XLIV, 29-36.
- WEISMAN, S. A. Observations on the contour of normal and tuberculous female chests, *ANN INT MED*, 1932, V, 907-911.
- WEISMAN, S. A. Contour of the chest in children. I According to age, *Am Jr Dis Child*, 1934, XLVIII, 502-506.
- WEISMAN, S. A. Contour of the chest in children. II According to weight and height, *Am Jr Dis Child*, 1935, XLIX, 47-51.
- WEISMAN, S. A. Contour of the chest in children. III Environment, *Am Jr Dis Child*, 1935, XLIX, 52-59.

- 2 PORTER, W T The physical basis of precocity and dullness, *Trans Acad Sci St Louis*, 1895 vi, 161-181
- 3 RIETZ, E Korperentwicklung und geistige Begabung, *Ztschr f Schulgesundheitspf*, 1906, xix, 65-98
- 4 GODDARD, H H The height and weight of feeble-minded children in American institutions, *Jr Ment and Nerv Dis*, 1912, xxxix, 217-235
- 5 COURTIS, S A Measurement of the relation between physical and mental growth, *Am Phys Educ Rev*, 1917, xxii, 464-481
- 6 GALTON, F Hereditary genius, 1869, Macmillan and Co, New York (Reprinted 1925), p 321
- 7 GOWIN, E B The selection and training of the business executive, 1918, Macmillan Co, New York, p 85
- 8 WOODROW, H Brightness and dullness in children, Chapter IV, *in Anatomical age*, 1919, J B Lippincott Co, Philadelphia, p 97-122
- 9 BALDWIN, B T, and STECHER, L I Mental growth of normal and superior children, *Univ Iowa Studies in Child Welfare*, 1922, ii, 1-61
- 10 SCAMMON, R E Chart presented to author by Dr Scammon

ACUTE LYMPHATIC LEUKEMIA IN A CHILD OF FOUR YEARS WITH A SEVERE GRANULOPENIC PHASE PRECEDING A REMISSION^{*}

By LEWIS B. FLINN, M.D., F.A.C.P., *Wilmington, Delaware*

THE study of blood dyscrasias has led to their division into a large number of groups, diseases and syndromes with a baffling nomenclature. The etiology of very few of these various subdivisions is proved and on this account there is no detailed classification which is generally acceptable. Ultimately perhaps a more definite etiological classification will be possible. The work of Castle¹ and his associates on the etiology of the macrocytic anemias has done much to clarify the confusion which existed in this field.

Search for the etiological agent in the leukemia group has so far met with less success. Here there is even more overlapping and confusion. Neither the infectious nor the neoplastic theory of the causation of the leukemias is entirely convincing although the acute leukemias rather suggest infection and the chronic type, tumor. Possibly the etiology ultimately may be attributed to some factor, or imbalance of several factors, now unknown but similar in principle perhaps to those discovered to be operative in macrocytic anemias. Gottlieb² for instance believes that the reticulo-endothelial system exerts an inhibiting influence upon the granulopoietic system and suggests the possibility that in certain states where granulopenia exists the normal balance between the two systems is upset. In the case he reported where the erythrocytes, granulocytes and hemoglobin were all greatly lowered, splenectomy was performed with the idea of relieving the reticulo-endothelial inhibition. The blood promptly returned to practically normal for a period, then, perhaps because the rest of the reticulo-endothelial system took up the splenic function and because of the additional strain of an acute infection, the anemia greatly increased and death occurred.

The protean nature of leukemia is well known. Jackson³ has emphasized the many and varied forms of malignant lymphoma. More recently since the number of cases of agranulocytosis has increased the differentiation of this condition from acute leukemia has occasionally given rise to diagnostic difficulties. Schultz⁴ in 1922 first presented agranulocytosis as a distinct clinical entity, perhaps a distinct disease. When one considers only such cases as he first described, those which are characterized by prostration, fever, necrosing stomatitis or pharyngitis, marked leukopenia, extreme decrease or absence of polymorphonuclear neutrophils, very little anemia and usually no platelet change—the clinical picture certainly suggests a distinct disease. Doan⁵ has described very thoroughly the various phases of this condition. Occasionally a rather similar clinical picture occurs fol-

^{*} Received for publication June 14, 1935

lowing known sepsis, also many cases have an insidious onset and the few which recover from the initial attack frequently have a recurrence of the disease. The author at the present time has under observation a case of two years' standing in which the initial attack occurred after small doses of radium for menorrhagia. Subsequent leukopenia in this case seemed to have a definite relation to the menstrual cycle and with reestablishment of the menses the blood count has remained normal. The precipitating factor in this syndrome of granulopenia, therefore, may vary greatly.

Several recent reports in the literature seem to point toward some actual connection between agranulocytosis and leukemia. Burkens⁶ reported a case with a leukopenia of 2,000 cells, all lymphocytic, which came on in conjunction with an infection of a foot. After the abscess was opened the blood picture returned to normal. One year later there occurred lymph node enlargement as well as enlargement of the liver and spleen. The white count showed mostly lymphocytes. No autopsy was reported. Easton⁷ reported a case of agranulocytosis which curiously enough preceded acute myelogenic leukemia. Potter⁸ and others reported similar cases. Rosenthal⁹ in discussing the various diseases exhibiting marked leukopenia cited no case, even with temporary recovery, in which there was such a severe leukopenia, neutropenia and thrombocytopenia as in the present case report. M. M. Strumia¹⁰ reported three cases of leukemia with a granulopenic phase. Two were granulocytic leukemias. The third simulates the case reported here except that the leukopenia was not so great and the child not so ill clinically, and at the onset in Strumia's case there was a definite infection in the form of an acute pericarditis with effusion, whereas in the author's case no infection could be demonstrated when the patient was first seen. Givan and Shapiro¹¹ reviewed 30 reported cases of agranulocytosis in childhood. Only four recovered, one of those, an infant of three months, had pyoderma, another had a recurrence every three weeks for 20 years, another had an acute upper respiratory infection just preceding the agranulocytosis. None of these had a leukopenia under 4,800. The fourth case to recover had a leukopenia of 600 and no granulocytes but had four months of purulent otitis media as an antecedent. Seventeen of the remaining 26 fatal cases apparently had no sepsis or demonstrable acute infection at the onset. From the data given these cases could not be differentiated from aleukemic leukemia or from a granulopenic phase of leukemia such as is reported in the case in this paper. Platelets when reported were diminished. Perhaps had these cases recovered from this granulopenic stage a definite leukemic picture would have followed.

CASE REPORT

Summary of History. The patient was a white girl, four years old. The mother's only other pregnancy had resulted in a previous miscarriage. The Wassermann tests on both mother and child were negative. The child had always been well except for pertussis and measles. The present illness was of gradual onset over

a period of three or four weeks with increasing weakness, lack of appetite, and slight irregular fever

Physical Examination, November 18, 1932 The patient was pale and did not look well. Temperature 102° F. Neither the ears, mouth, teeth nor pharynx appeared unusual. There was a slight discharge from both nostrils. The mouth, teeth and pharynx showed nothing abnormal. The tonsils were only slightly enlarged. There were numerous enlarged cervical lymph nodes, epitrochlear and axillary nodes were palpable, inguinals not definitely enlarged. The thyroid was not enlarged.

The lungs were clear throughout. The relative cardiac dullness extended 5.5 cm to the left in the fifth interspace, 2.5 cm to the right in the third interspace. Transverse diameter of the heart was 8 cm. Just inside the apex there was a blowing systolic murmur, not well heard in the axilla or at the pulmonic area. The second sound was accentuated. The spleen was definitely palpable about 2 cm below the costal border. The liver was not definitely felt. The abdomen and the extremities were otherwise negative.

The blood picture was as follows: Hgb 32 per cent (Dare). Red blood cells, 2,000,000. White blood cells, 11,200. Polymorphonuclear leukocytes, 20 per cent. Small lymphocytes, 64 per cent. Large lymphocytes, 12 per cent. Myelocytes, 4 per cent. There was moderate anisocytosis and slight poikilocytosis. The platelets were reduced in number.

First Hospital Admission, November 20 to 23, 1932. Laboratory data. The coagulation time was three and a half minutes. The bleeding time was four minutes. The Van den Bergh test was negative. Fragility test: hemolysis began in 0.42 per cent sodium chloride solution and was complete in 0.32 per cent. The blood picture was essentially the same as given above.

A transfusion of 200 c.c. of citrated whole blood was given the day after admission. At this time the temperature was 104.4° F and there was marked swelling of the posterior cervical lymph nodes on both sides. The temperature after ranging from 102° to 103° for two days dropped to 99° on the third day, coincident with a typical German measles eruption and prompt subsidence of the swelling of the post-cervical lymph nodes. During this episode the white count fell to 3,600 cells with only 5 per cent polymorphonuclear leukocytes. The patient was removed from the hospital and for two days had no fever. A necrotic ulcer then developed in the upper pole of the left tonsil, the temperature rose to 102°, the child became critically ill and returned to the hospital December 2, where she stayed until January 23, 1933.

The white blood cells numbered 10,140, with 12 per cent polymorphonuclear leukocytes. A blood transfusion of 200 c.c. was given immediately. Two days later the prostration had increased, the ulcer was becoming larger and deeper, the temperature ranged from 104° to 105° and the white cell count dropped to 3000 with 6 per cent polymorphonuclear leukocytes. A transfusion of 200 c.c. of blood was again given. The white cells dropped to 2650 and then to 1300. The red cells dropped to 1,500,000 without marked change in size or shape. The platelet count was 10,500.

At this time 0.7 gm of pentnucleotide was given twice daily, once intravenously and once intramuscularly. Necrosis began at the left corner of the lower lip. After nine days of pentnucleotide therapy the white cells dropped to 700 with 9 per cent polymorphonuclear leukocytes. The small lymphocytes, the predominant cells, were immature with unusually large nuclei. Chart 1 shows the detailed blood studies as well as the essential clinical findings and therapeutic measures. At this time bilateral otitis media and bronchitis developed. The child was so critically ill that no hope was given for her recovery. Finally the white cells began to rise gradually from 700 on the twelfth day of pentnucleotide therapy to 2000 on the sixteenth day, December 21. The reticulocytes rose to 3 per cent on December 20. The temperature which had ranged between 102° and 105° gradually came down to 100° (rectal) on the

twenty-first day and on that day she coughed out her sloughed left tonsil. The hemoglobin and red cells had increased to 59 per cent and 3,200,000 respectively. The tenth transfusion was performed on December 24. On the twenty-fifth the pharynx was completely healed and the subsequent improvement seemed truly miraculous. In a few days she was sitting up, had a ravenous appetite and on discharge, January 23, 1933, was able to walk alone. The entire blood picture including the platelet count had returned to normal.

COMMENT

The diagnosis of German measles rather than a toxic eruption seemed justified because of the sudden exacerbation of fever lasting three days, coincident with enlargement of post-cervical lymph nodes, pharyngeal injection, appearance of a typical eruption on the third day as the fever subsided, followed by prompt subsidence of the lymph node swelling. There was also a transient leukopenia at this time.

The necrotic ulcer of the left tonsil started during this attack of rubella. On the seventeenth day of observation during the second hospital admission the fever increased, leukopenia became more pronounced and the child became so desperately ill that no one who saw her from the twenty-second day to the thirty-second day expected her to recover. It is interesting to note that blood transfusions had apparently no good effect upon the granulopenia until the leukocytes began to increase 12 days after pentnucleotide therapy was started. The latter was given both intramuscularly and intravenously. When improvement did set in, the hemoglobin and erythrocytes increased more rapidly than could be explained by transfusions alone. Our observation of this case and findings in several other cases of agranulocytosis is in accordance with Jackson's^{12, 13} impression that if blood transfusions have any effect on the leukopenia in these cases they increase it. Doan⁵ suggests that there may be a temporary decrease in the leukocyte count followed by a rise due to nucleotide set free by destruction of the transfused cells. Reznikoff¹⁴ takes a similar view in discussing nucleotide therapy in these cases. It is our policy then to transfuse not on account of the leukopenia but solely to relieve anemia.

Interim Progress January 2, 1933 to May 15, 1933. For three months the patient was exceptionally well at home and according to the mother, more active and stronger than ever before. There was a gain of about five pounds in weight. The left ear, however, continued to discharge. Blood counts during this period were as follows:

	Hgb (per cent)	R B C (millions)	W B C	P M N (per cent)
2/13/33	71	4.1	11,600	53
3/1/33	78	4.2	10,200	54
3/14/33	80	4.2	11,200	42

On March 15, 1933 some swelling was noted about the joints and small bones of the hands and the child complained of bone pains in the wrists, phalanges and femora. Irregular fever was again found present.

On April 30, 1933 an acute follicular tonsillitis developed. The stub of the previously sloughed out left tonsil became slightly enlarged. Temperature ran between 102° and 104° F for three days. Blood counts at about this period were as follows

	W B C	P M N
4/28/33	18,000	30
5/6/33	18,000	20
5/11/33	65,000	3

The bone and joint pains and irregular fever continued, and on May 15 the patient was readmitted to the hospital.

Third Hospital Admission May 15 to July 15, 1933 During this final hospital admission the clinical course of the illness was marked by irregular fever between 99 and 105° F. There was some swelling during the first three days of the cervical and axillary lymph nodes but after this time no lymph gland enlargement was ever made out. The spleen was at no time in this period palpable.

The fusiform swelling of the phalanges, and particularly of the proximal phalanx of the second digit on each hand, gradually increased. Roentgenograms at various times showed thinning of the cortical zone and rarefaction in the bones of the hands, the radius, ulna and femora. (See figures 1 and 2.)

Swelling developed in the region of the left mastoid and on June 2 mastoidectomy was performed under gas anesthesia. A variety of organisms was recovered from the mastoid cells, a blood culture at this time remained negative. Recovery from the operation was uneventful.

A vesicular eruption simulating herpes zoster appeared over the left thigh and flank, it cleared up within a week. This finding is interesting in the light of a report of Craver and Haagensen¹⁵ who found seven cases of herpes zoster in 329 cases of Hodgkin's disease, lymphosarcoma and leukemia. They call attention to the fact that such an incidence is considerably greater than that found in any general hospital.

The general trend of the illness was downward. Fever continued though the lungs remained clear and there was at no time any evidence of endocarditis. In the last two or three days of life a large rapidly advancing necrotic lesion developed in the pharynx and also a second similar lesion about the anus. Death occurred on July 15, on the two hundred forty-first day of observation.

Laboratory Studies The red blood cell count fell from 4.7 million to 1.7 million the day before the patient's death. The hemoglobin likewise fell from 82 to 34 per cent. The white blood cell count was taken daily and showed marked variations which were not explicable by the apparent clinical condition. The total wbc count usually varied between 9,000 and 56,000. Two days before death, however, it was 32,700 and on the day preceding death it had fallen to 1,600. The differential counts showed that the lymphocytes constituted between 92 and 100 per cent of the total white cells, most of the lymphocytes were immature. The polymorphonuclear leukocytes ranged from none to 8 per cent of the total.

Platelet counts revealed a total absence of platelets, none were ever found. The reticulocyte count was always below normal. This was in contrast to the first admission. The coagulation time was not increased. The tourniquet test would occasionally cause petechial hemorrhage. The fragility test was not markedly changed, hemolysis began at 0.38 per cent and was completed at 0.32 per cent.

The results of therapy, given without expectation of cure but in the hope of at least temporary improvement, were disappointing. Seven transfusions were carried out in this admission, making a total of 17 in all. For 26 days pentnucleotide was administered in doses of 0.7 gm to 1.4 gm daily. Reactions to pentnucleotide were at times marked, characterized by vomiting with the appearance of mild general



FIG 1 Roentgen-ray demonstrates marked rarefaction of bones, particularly marked in the lower end of both femora. At autopsy the cortex of the rarefied area in the left femur was of egg shell thinness.

shock. Several abscesses developed at the site of intramuscular injections and when opened the purulent exudate on smear showed polymorphonuclear leukocytes and staphylococci. Following the pentnucleotide two series of daily injections (one of four and one of seven days) of leukocytic cream were given. The dosage was 8 c.c. No clinical or hematological effect was noted.

Beginning on July 6, Addisim was given in 10 c.c. doses three days apart. It had been suggested by Morris¹⁰ and his coworkers that this material was of advantage in agranulocytic angina and was under trial in leukemia. In the present case it produced no demonstrable effect.



FIG 2 Roentgen-ray demonstrates rarefaction of both radius and ulna and of small bones of the hand

AUTOPSY REPORT

Douglas M. Gay, M.D., Pathologist, Delaware Hospital

The body is that of a fairly well developed and slightly emaciated white female child 103 cm in length. Rigor mortis is present in the jaw only. Dependent parts are livid. The eyes, ears and nose are normal. The pupils are round, regular and equal, each measuring 0.4 cm in diameter. A superficial ulcer about 0.5 cm in diameter is present on the left side of the dorsum of the tongue. Other small superficial ulcers are present on the palate. The pharynx and right tonsillar region are necrotic and appear to be covered with a soft light brown material. An irregular opening extends through the skin over the left mastoid region into the bone and is filled with a foul smelling brown material. A longitudinal incision 2 cm long is present on the outer aspect of the right thigh. This extends into the subcutaneous tissue and is filled with a small gauze. The anus and surrounding tissue are dark red brown in color and present several bullae filled with light brown fluid.

Peritoneal Cavity Surfaces smooth and glistening No adhesions or free fluid present Mesenteric lymph nodes are soft, red, and moderately enlarged The largest of these measures about 1 cm in diameter *Pleural Cavities* Surfaces smooth and glistening No adhesions or free fluid present *Pericardial Cavity* Surfaces smooth and glistening No adhesions or excess of fluid present

Heart Normal in size, shape and position Epicardium is smooth and transparent Myocardium homogeneous, dull red and firm in consistence Endocardium is thin and transparent Cavities, valves and coronaries are grossly normal *Lungs* Normal in shape and size Soft and crepitant throughout Multiple sections reveal normal pale pink lung tissue Tracheo-bronchial lymph nodes are not enlarged *Spleen* Weight 174 grams Moderately enlarged Normal in shape and firm in consistence The capsule is thin over a smooth dark purple surface On section the spleen is a similar dark purple color and markings are not readily made out A small amount of pulp scrapes away *Pancreas* Normal in size, shape, color and consistence *Liver* Weight 1250 grams Moderately enlarged The edges are rounded, capsule is thin over a smooth red brown surface On section the liver is a similar red brown color and the markings are not distinct The enlarged size of the liver is apparently due to an increase in substance rather than congestion The gall-bladder is not remarkable *Gastrointestinal Tract* Grossly normal throughout Peyer's patches are not prominent *Adrenals* Normal in size and shape Medullary portion is very thin Cortical portion is light yellow brown in color *Urinary Organs* The kidneys are about twice normal size The capsule strips spontaneously from a dark red surface On section the cortex measures 0.6 cm in average thickness and is dark red in color The medullary portion is pale red gray The calices, pelves, ureters and bladder are normal *Genital Organs* Grossly normal *Aorta* Normal *Lymph Nodes* Superficial lymph nodes are slightly enlarged, only in the left cervical region Mesenteric nodes are slightly enlarged, soft and red The retro-peritoneal lymph nodes in the lumbar region are moderately enlarged, the largest being 2 cm in diameter This group of nodes presents a mass of nodules which are firm and pale gray in color A series of dark red nodes extends along the posterior portion of the rectum These average 0.5 cm in diameter and are soft in consistence The tracheo-bronchial lymph nodes are not enlarged *Bones* The ribs are brittle and the bone marrow is pale gray red in color and the sternal marrow is also pale red gray The lower end of the left femur is minutely roughened and the periosteum appears to be elevated a distance not greater than 0.1 cm by a soft red gray infiltration The cortex of this portion of the femur is very thin and the marrow cavity is large The vertebral marrow is yellow in color, fatty in consistence and contains numerous small hemorrhages Other bones are not investigated

Microscopic Notes *Heart* The myocardium is not remarkable A thin layer of cells is infiltrating beneath the pericardium These cells are of medium size, round in shape and resemble the tumor cells described below *Lung* Normal *Spleen* Numerous large mononuclear cells containing orange brown granules (hemosiderin) are distributed throughout There are also numerous large phagocytic cells containing cellular debris As far as can be made out the phagocytized material consists of nuclear and cytoplasmic remnants Masses of tumor cells are distributed around the small arteries and trabeculae The detailed description of these cells is given under lymph nodes A few foci also contain cells resembling eosinophilic myelocytes *Pancreas* An infiltration of tumor cells is present in the stroma around the larger blood vessels Otherwise the organ is normal *Liver* Small masses of tumor cells are present in every portal space The liver cells are faint staining, the cytoplasm is granular and the nuclei are sharply outlined but apparently deficient in chromatin *Adrenal* Groups of tumor cells are present in the medullary portion and around some of the blood vessels in the capsule *Kidney* The cortex appears to be

greatly thickened by the presence of tumor cells and diffuse hemorrhage. The perivascular distribution of tumor cells noted in the other organs is especially prominent in the kidney. The tubules appear to be surrounded by masses of hemorrhage and the glomeruli by masses of tumor. There is no evidence of tumor within the glomerular capsule. The medullary portion of the kidney is not remarkable. Perivascular groups of tumor cells are present in the loose connective tissue near the papillae. *Aorta* Normal. *Intestine* The one section studied is not remarkable. *Lymph Nodes* Sections of four lymph nodes from various parts of the body show a similar picture varying in degree. Only a slight suggestion of the follicular structure of the node is present. The sinuses, however, are easily made out. These contain numerous large mononuclear cells and many smaller cells interpreted as tumor. The picture is not characteristic of lymphoblastoma, in that the follicles may occasionally be discerned. The sinuses are not packed with the tumor cells and the cells themselves are not of the usual appearance. The average tumor cell is about 14 microns in diameter. It is round with dark red cytoplasm. The nucleus is round and contains a moderate amount of chromatin. Mitotic figures are seldom found. The large phagocytic cells described elsewhere are also present in the lymph nodes. The general appearance of these cells is similar to the tumor cells, although the former are larger and the cytoplasm tends to be brighter red. The phagocytized material consists of cellular debris and red blood corpuscles. A few cells resembling normoblasts and others resembling myelocytes are present in the sinuses. There appears also to be a small amount of blood in the sinuses of some of the nodes. A few tumor cells are apparently present in the capsule. *Bone* A section of the femur shows a heavy infiltration of tumor cells between the bone and the periosteum. The tumor cells also extend above the periosteum among fibers of striated muscle. The bone marrow shows a diffuse infiltration with tumor cells although an abundance of fat tissue remains. There is very little evidence of hematopoiesis, although an occasional polymorphonuclear leukocyte is present. There are numerous small hemorrhages. The picture is essentially the same in the marrow from the sternum, ribs, femur and vertebrae.

DISCUSSION

The clinical picture and blood studies when the patient was first seen suggested the possibility of a leukemia or a severe secondary anemia, possibly due to some previous infection. None of the usual physical signs of leukemia presented themselves, however, and except for the high percentage of small lymphocytes the whole picture in the second week could be explained on the basis of a secondary anemia. The attack of German measles was the precipitating factor in the onslaught of the severe, almost fatal episode of agranulocytosis. Apparently this was relieved by nucleotide therapy with supporting blood transfusions. Differentiation between an aplastic anemia and malignant neutropenia was difficult for a time. It is interesting that when the blood picture returned to normal the platelets did also. The two months of almost perfect health following the second hospital admission must be considered in the light of later developments, as merely a remission of leukemia. It is difficult, however, to consider the leukopenic episode as entirely leukemia unless primary agranulocytic angina shall be found to be merely one form or phase of leukemia. Certainly they both may have remissions but certainly too, leukemia with leukopenia rarely if ever reaches

the extreme cited in this case without at once ending fatally. During the last admission, even up to 48 hours before death the child never appeared as ill clinically as in the previous leukopenic state. It is interesting to note that the first phase of the disease was preceded by an attack of rubella, a disease usually associated with leukopenia, and that the onset of the hyperleukocytic leukemia phase was coincident with an attack of follicular tonsillitis, a disease usually associated with leukocytosis.

SUMMARY

I The protean nature of leukemia is briefly discussed particularly in regard to its possible relationship with primary agranulocytic angina.

II An unusual case of acute lymphatic leukemia of 8 months' duration in a child of four years is reported in detail, the salient features of which are

(a) An extreme agranulocytic phase followed by a remission of two months.

(b) A typical terminal leukemic phase without demonstrable lymph node enlargement except at autopsy.

(c) Marked leukemic bone changes, clinically, by roentgen-ray and at autopsy.

(d) Herpes-zoster.

(e) The leukopenic phase was apparently precipitated by an attack of rubella, a disease usually associated with leukopenia, and the final leukocytic or leukemic phase was apparently precipitated by an attack of acute follicular tonsillitis, a disease usually associated with leukocytosis.

REFERENCES

- 1 CASTLE, W. B. Etiology of pernicious anemia and related macrocytic anemia, *ANN INT MED*, 1933, vii, 2-5.
- 2 GOTTLIEB, R. Myeloid insufficiency, *ANN INT MED*, 1934, vii, 895-902.
- 3 JACKSON, H., JR. Some little appreciated aspects of malignant lymphoma, *Trans Am Clin and Clin Assoc*, 1932.
- 4 SCHULTZ, W. Über eigenartige Halserkrankungen und Defekt des Granulozytensystems, *Deutsch med Wchnschr*, 1922, xlviii, 1495.
- 5 DOAN, C. A. Neutropenic state—significance and therapeutic rationale, *Jr Am Med Assoc*, 1932, xcix, 194-202.
- 6 BURKENS, J. C. J. Agranulocytose, gevolgd, door leucaemie, *Nederl Tijdschr v Geneesk*, 1931, lxxv, 2722, *Abstr Am Jr Cancer*, 1932, xvi, 499.
- 7 EASTON, J. H. Acute myelogenous leukemia preceded by agranulocytosis, *Lancet*, 1930, ii, 1394.
- 8 POTTER, H. W. Myelogenous leukemia with an aleukemic stage simulating agranulocytosis, a case report, *Va Med Month*, 1932, lviii, 739-743.
- 9 ROSENTHAL, N. Hematological aspects of agranulocytosis and other diseases accompanied by extreme leukopenia, *Am Jr Clin Path*, 1931, i, 7-32.
- 10 STRUMIA, M. M. Personal communication to the author. Reports to be published.
- 11 GIVAN, T. B., and SHAPIRO, B. Agranulocytosis in childhood, *Am Jr Dis Child*, 1933, xlv, 550-560.

- 12 JACKSON, H, JR, PARKER, F, JR, RINEHART, J F, and TAYLOR, F H L Diseases of lymphoid and myeloid tissues, treatment of malignant neutropenia with pentose nucleotides, Jr Am Med Assoc, 1931, xcvi, 1436-1440
- 13 JACKSON, H, JR, PARKER, F, JR, and TAYLOR, F H L Nucleotide therapy, Am Jr Med Sci, 1932, clxxiv, 297-304
- 14 REZNIKOFF, P Nucleotide therapy, Jr Clin Invest, 1930, vi, 381-391
- 15 CRAVER, L F, and HAAGENSEN, C D A note on the occurrence of herpes-zoster in Hodgkin's disease, lymphosarcoma and the leukemias, Am Jr Cancer, 1932, xvi, 502-514
- 16 MORRIS, R S, RICH, M L, SCHIFF, L, FOULGER, J H, and FELSON, H Observations on Addison in diseases of the blood, ANN INT MED, 1933, vi, 1536-1545

CASE REPORTS

AN INSTANCE OF POSSIBLE CIRRHOSIS OF THE LIVER INDUCED BY A HAIR TONIC CONTAINING CARBON TETRACHLORIDE *

By B B VINCENT LYON, M D , D Sc , F A C P , *Philadelphia, Pennsylvania*

THERE are many substances now known to produce definite hepatic injury, such as chloroform, various arsenicals, various members of the quinoline series such as cinchophen, etc. As a result of numerous publications regarding their danger the medical profession has learned to exercise greater caution in their use.

Because of the increasing popularity of its use as a cleaning fluid by the general public, carbon tetrachloride (and trade marked cleaning agents containing it) should also be included in this group. Indeed, in current interest, it now leads the list of chemicals which can produce liver injury.

For many years it has been considered an industrial hazard. There is no doubt that the large dry cleaning establishments now use greater care to protect their employees because of the increasing number of medical publications which have appeared. But the general public needs continued caution as to its danger.

Its poisonous effect can reach the liver by inhalation through the lungs by absorption through the injured skin, or—as occurs less frequently—by absorption from the digestive tract when it is administered orally. In addition to producing liver damage, it injures the kidneys, upsets the gastrointestinal tract and affects the hematopoietic and the central nervous systems.

Its absorption by the body in large doses produces acute symptoms involving these organs. Some deaths have followed the absorption of overdoses. In the liver there is produced an acute toxic necrosis of the hepatic cells, with a clinical picture and pathological findings similar to those in acute yellow atrophy, or acute hepatitis. The kidneys are affected and show the pathological changes of nephrosis (hemorrhage and fatty degeneration) and albumin and casts appear in the urine, associated with renal subfunction, the gastrointestinal tract becomes inflamed, and nausea, vomiting and diarrhea are commonly observed, the central nervous system is affected, and profound dizziness, syncope, and temporary unconsciousness may occur.

In smaller doses, repeated over long periods, the acute manifestations are less conspicuous but, regarding the liver, the potentiality of carbon tetrachloride is in the production of cirrhosis of the liver. It has been suggested (Davis) that retrograde changes also take place in the kidneys, the hematogenic organs, and in the central nervous system after continued exposure to carbon tetrachloride of low concentrations.

Lamson and his co-workers, and Bollman and Mann, and others have found that by the repeated administration of this substance in appropriate doses for several weeks, they can experimentally produce a condition of the liver of the dog similar to cirrhosis as seen in man.

Carbon tetrachloride (CCl_4) is a saturated chlorine derivative of methane (CH_4) or marsh gas. It is an extremely volatile substance of high specific

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935

gravity, 1.599, a boiling point of 170.6°F , and a vapor density of 5.33. Thus, this drug is chemically related to chloroform (CHCl_3) which is also well known for its effect in producing liver injury.

Davis states that the most frequent uses of carbon tetrachloride now fall into eight groups:

- 1 As a solvent in the rubber industry
- 2 As a solvent in the chemical and drug industry
- 3 As a solvent in the paint industry
- 4 As a cleansing agent in the dry-cleaning industry
- 5 As an occluding and non-oxidizing agent in fire extinguishers
- 6 As an anthelmintic for parasites, notably hookworm, in the practice of medicine
- 7 In machine shops for the removal of grease
- 8 As a dry shampoo in the hair dressing industry, especially in Europe

A number of cases of acute poisoning following the use of a shampoo containing carbon tetrachloride have been reported, and an occasional death therefrom. Kionka states that the drug is not absorbed through the *uninjured* skin even when applied in large quantities, but Davis says that "carbon tetrachloride extracts the fats from the skin and produces a dry condition which favors absorption and also initiates a dry dermatitis, causing the skin of the hands to crack." Absorption in this manner, as well as by inhalation, might therefore apply to our patient who used a hair tonic containing this drug for a seborrheal alopecia. It might be added that dermatologists in many localities, here and abroad, use this drug for this and other dermatological conditions.

An exact analogy between the histories of carbon tetrachloride poisoning as contained in the literature and the history of the patient here reported is difficult to find. This is due to the fact that in the majority of reported instances poisoning with carbon tetrachloride has been an acute phenomenon, whereas in the present instance the intoxication was in the form of minimal but persistent amounts just sufficient to produce a low gradual intoxication with slowly progressing manifestations. Nowhere in the literature could we find an instance of chronic poisoning in which a similar use of this drug occurred. Knud Møller reports several instances of patients being overcome with acute dizziness and vertigo and temporary unconsciousness after being shampooed with carbon tetrachloride. Presumably the amount of the drug rubbed into the scalp and inhaled by his patients was much greater than occurred in our patient. It is probable that after such acute effects Møller's cases did not return for further shampoos nor was there in his report any long time "follow-up" for after-effects.

But why did not the applier of the shampoo suffer equally to the recipient? The hairdresser in giving a treatment theoretically should absorb as much of the drug through the skin (hands) and by inhalation, and much more frequently when carbon tetrachloride is thus used routinely. Does this not suggest that an individual's susceptibility may play an important part? In our patient we found unusual susceptibility to several drugs to belladonna or atropine, to caffeine in coffee and to nicotine or the volatile oils in tobacco.

In view of the fact that carbon tetrachloride is used in shampooing particu-

larly in Europe, one would expect to find similar reported cases. We believe that the absence of such reports is the result of a failure to diagnose the ill effects produced by long application of this chemical. There are already sufficient reports in the literature indicating, both experimentally and chemically, the effects of the absorption of this poison through the skin, particularly when applied repeatedly and over a long period of time, and particularly when reinforced by inhalations during the period of application to the skin.

CASE REPORT

Mr S first came under our observation in November 1924 when he was 34 years of age. Over the next 10 years he has been seen many times, on occasions at frequent intervals and at times after an interval of several months. His family and past medical history are unimportant.

His chief complaint has been a diffuse aching pain across the upper abdomen which was first noticed in 1924 and which occurred five to seven hours after his evening meal. It spread upward over an inverted fan-shaped area and centered chiefly in the substernal region. At times the pain-distress was described as a burning sensation, at times as a sense of constriction. It would frequently waken him from sleep between 1 00 and 3 00 a.m., would continue for two to four hours, and was best relieved by heat from an electric pad. At other times the pain was replaced by a sense of upper abdominal fullness and tightness, with distention requiring loosening of belt and clothing. Subsequently (1928 to 1933) he intermittently complained of mild nausea and a distaste for and discomfort after certain foods, especially too heavy protein or fat meals or too bulky vegetables such as cabbage. By degrees certain symptoms, interpreted as toxic effects involving the nervous system, developed, such as loss of mental alertness and concentration, moodiness, nervous irritability, undue fatigability, restless sleep, and mild nausea.

Physical examination in 1924 was not informative save for his sallow color and slight scleral icterus. His liver and spleen were of normal size. There were no telangiectases or hemorrhoids. Cardiovascular disease was not present.

It was not until 1930 that his liver became palpably enlarged to three inches below the costal margin, without explainable cause. He was not addicted to alcohol. There were no foci of infection except in the tonsils and several tooth roots but these were removed during or before 1930, without clinical improvement.

Between 1924 and 1930 it was difficult to feel that this patient was a sick man and we wondered how much neuropsychic disturbance was actually present. However, the patient himself from his own subjective symptoms, which continued despite various plans adopted to control them, repeatedly declared that they were very real and not influenced by his imagination. During this six year interval he had been carefully studied and the following findings were developed:

- 1 Gastrointestinal roentgen-ray series by Dr George Pfahler and Dr Willis F Manges were not in agreement as to a possible cholecystitis, and biliary drainage evidence did not support this diagnosis.
- 2 Evidence by roentgen-ray of moderate colon stasis, but without subjective constipation.
- 3 Nine fractional gastric analyses indicated a persistent achlorhydria, interpreted as a functional disturbance rather than progressive atrophic gastritis because of preservation of rennin and renninzymogen.
- 4 A mild degree of toxic nephritis was diagnosed because of numerous hyaline casts, a trace of albumin and but 50 per cent elimination of phenolsulphonephthalein in two hours after intramuscular injection. Calcium oxaluria was present on many occasions.
- 5 A moderate degree of secondary anemia.

In 1930 a suspicion was entertained that these clinical findings might represent the inaugural stages of prepernicious anemia despite absence of stomatitis or noteworthy changes in his blood count. But in 1931 this view was discarded in favor of an early stage of compensated hepatic cirrhosis because of the enlarging liver and particularly so because the patient complained of a marked sense of tenderness and overdistention in the liver region two to three hours after taking tetraiodophthalein during a third roentgen-ray study by Dr J Gershon-Cohen. The gall-bladder was found to be functioning normally and there was no roentgen-ray evidence of gastrointestinal pathology.

However, neither liver function tests nor blood chemistry have been of much help in this case in estimating liver disease or dysfunction even during the period when the enlarged liver (1930 to 1931) receded to normal size (1932 to 1933) and subsequently became smaller than normal (1934 to 1935).

The direct Van den Bergh reaction has been negative on seven occasions, positive delayed direct reaction occurred only once. Quantitative bilirubin has been above 0.3 mg per 100 cc only twice, reaching 0.6 mg six days after a tetraiodophthalein dye test in March 1933 and 0.37 mg in January 1935, at which time the icterus index registered 12.5 units and urobilinogen was present in a dilution of 1 to 40. The patient declined to take a bromsulphalein dye test because of the excessive tenderness of the liver region which had previously followed tetraiodophthalein.

His blood sugar has been constantly on the low side of normal and below normal on two observations, uric acid values have been constantly on the high side or slightly above those for normal, cholesterol readings have been constantly above normal values, urea and non-protein nitrogen were generally above normal.

The amount of liver bile excreted and collectible by duodenal drainage has for many years impressed us as an aid in estimating the function of liver excretion. We have found first, that healthy young adults yield 250 to 300 cc of "C" bile (liver fraction) over a three hour period of actual drainage time, with 200 cc representing low normal, second, that in patients with damaged livers (except shortly after an obstructive jaundice has been overcome) recoverable "C" bile drops to less than 150 to 200 cc. In this patient, during 1924 and 1925, the "C" bile averaged slightly over 50 cc. Under treatment (carbohydrate diet, decholin and biliary drainage) it increased to 205 cc but after an interval of three years dropped back to 145 cc.

Between 1930 and 1933 our patient's teeth showed progressively interesting changes in pronounced gum recession on the buccal surface (notably Nos 28, 29, 30 and 31) and by 1933 an erosion of the enamel of the central and lateral incisors had now penetrated through the enamel, with marked flattening of the cusps of the remaining teeth. Coincidentally with this, an arcus senilis noted in 1930 had by 1933 noticeably increased. His gums and mucous membrane were paler than was consistent with his blood count. His color was constantly sallow and his breath distinctly heavy.

It was now evident to us that this patient was suffering from some form of slow intoxication the etiology of which was not apparent at the time of our original examination nor over a period of eight years of discomfort.

In 1933 our attention was attracted to a report of hepatic disturbance following the inhalation of carbon tetrachloride and the possibility of this etiological factor was investigated. It was found that our patient had been using, since 1919 for a seborehéal alopecia, a hair tonic and scalp lotion containing precipitated sulphur suspended in carbon tetrachloride, according to the formula of Prof R Sabouraud, the distinguished dermatologist of Paris, and still advocated by him in his various textbooks. This was applied nearly every evening for two or three minutes in a well ventilated bathroom, but it will be noted that untoward symptoms did not develop until 1924, five years later. Despite adequate ventilation the odor of carbon tetrachloride would

persist in his bathroom for an hour after the use of this drug. In addition, it was developed on questioning that carbon tetrachloride was also used as a cleaning agent in his office and that the absorbent cotton, still moist with this chemical, was frequently thrown into the waste basket directly under the nose of our patient. Hence the slow intoxication by this poison absorbed through skin and lungs was accounted for.

In December 1933 we advised that this hair tonic, used more or less regularly for 14 years, should be permanently discarded. Coincidental with this, there occurred (1934 to 1935) the first genuinely subjective improvement in abdominal discomfort and a return of increasing amounts of free hydrochloric acid during gastric analysis and an improvement in blood chemistry. His prior subjective symptoms, as already noted, and a dull ache in recent years chiefly over the liver region, gradually disappeared. He has a more constant sense of well being but he is still unable to "stomach" all foods. He has lessened fatigability but he is still unable to work at high tension without developing an "all gone" sensation in the epigastrium. The mechanism of this can, at most, be but theoretically explained but it may be associated with his hypoglycemia or it is possible that injury to his autonomic nervous system occurred at some time during the period of his slow poisoning.

Objectively, in January 1935, his sallow color is improved. There is no skin and but slight scleral jaundice. He is much more alert, and he seems (and says he is) less "toxic." His teeth are as noted before, except that all cusps have now entirely disappeared. His liver is still definitely smaller than the average normal for his sthenic build. To percussion, the upper border lies at the top of the seventh rib in both the midclavicular and midaxillary lines, and the lower edge does not extend below the rib border. To palpation, at the height of deep inspiration, the liver edge cannot be felt except a small portion of the outer edge of the right lobe. The patient evinces tenderness in forcibly palpating for the liver edge. There are no telangiectases, ascites, or movable dullness, nor have there ever been. So, from start to finish, if the changes in the liver size, the slightly altered blood chemistry and serology, the diminished liver excretion to duodenal drainage, and the somewhat vague symptoms can be considered due to a possible hepatic cirrhosis, it has, except for the subjective disturbances, at all times been well compensated.

Mann and Bollman have had a large experience in studying the effects on the liver of carbon tetrachloride administered by mouth and by inhalation. They find * it difficult to make a direct statement as to the effects of this drug without considerable qualification. They urge careful differentiation between the hepatic cirrhosis of carbon tetrachloride and its acute necrotic effects on the liver which are more like acute yellow atrophy. They find that the cirrhosis is reparative in nature and in the absence of acute effects they are unable to detect any metabolic or functional alterations except in extreme cases. Unfortunately there are usually some renal impairment and disturbances in the gastrointestinal tract which frequently further complicate the picture of carbon tetrachloride poisoning.

Bollman and Mann believe that the alterations of metabolism following acute injury of the liver by such poisoning depend upon the extent of damage to the liver. Bilirubinemia, dye retention, decreased galactose tolerance, etc., are usually present. They find the changes in blood and urine nitrogen are less marked. A slight increase in the uric acid content of the blood is usually found, but no change can be proved in the total non-protein nitrogen, urea, amino acids, ammonia or creatinine, although at times they noted a slight elevation of amino acids and low urea values. The urine may show an increase in uric acid excretion and some increase in amino acids.

* Personal communication

They do not mention the significance of increased excretion of calcium oxalate in the urine which was noted in the case we are reporting, and which we have noted in cases of suspected liver damage previously studied

Our patient's definite hypersensitiveness to tobacco smoke was interesting and raises the query as to where in the body is nicotine, or the essential oils or the potassium nitrate in the tobacco or paper of cigarettes, destroyed. Is it in the liver? On closely questioning our patient in regard to such symptoms as he earlier attributed to tobacco smoke, he states that he had not shown any unusual effects in smoking 20 to 30 cigarettes a day until several years after he became exposed to the slow intoxication by carbon tetrachloride as set out above, but subsequently, after being exposed to large quantities of tobacco smoke, as in a business meeting or a smoker, for example, for three or four days thereafter he noted a dull ache in the upper abdomen more frequently in the liver region. This may have been present earlier in his illness than he remembered but he did not attribute it to smoking until a later date at which time he discontinued its use. For several months thereafter he was temporarily relieved of this symptom but he clearly observed recurrences when he attempted to resume moderate smoking or when exposed to heavy or even mild smoking by others.

SUMMARY

In our patient, aside from the changes in the size of the liver, we observed as possible effects of chronic carbon tetrachloride poisoning

- 1 Certain symptoms and signs affecting the gastrointestinal tract and the central nervous system

- 2 A slight reduction of hemoglobin (70 to 75)

- 3 A slight reduction of blood pressure (100 to 110 systolic)

- 4 A tendency to hypoglycemia (75 to 85 mg)

- 5 Increased blood uric acid, a substance normally destroyed by the liver (4.3 to 5.2 mg)

- 6 Hypercholesterolemia (190 to 345 mg)

- 7 An absence of gastric hydrochloric acid (functional)

- 8 A hypersensitiveness to nicotine or volatile oils in tobacco

- 9 Changes in dental enamel and atrophy of the gingiva

All of these, save the last, were appreciably ameliorated after stopping the use of the hair tonic containing carbon tetrachloride

We again admit the inability to consider this case as other than a "possible instance" of hepatic cirrhosis produced by very slow intoxication, but we feel that it should be reported because of the difficulty experienced in arriving at this diagnostic impression

It is probable that borderline cases of chronic intoxication from one or another poison are not so rare as they are unrecognized. By "borderline," we refer to such cases as become diagnostically clear cut as a disease only after gross damage to the viscera has occurred. Then, as a rule, gross chemical changes can be determined by laboratory studies. The real danger lies in classifying many such borderline patients as neuropsychopaths, leading to a too early abandonment of the search for causative factors

REFERENCES

- COLMAN, H C, and MARSHALL C R A dangerous dry shampoo (carbon tetrachloride), *Lancet*, 1907, i, 1709
- LAMSON, P D, and others *Bull Johns Hopkins Hosp*, 1923, *xxvii*, 107
- LAMBERT, S M Carbon tetrachloride in the treatment of hookworm disease, *Jr Am Med Assoc*, 1923, *lxix*, 526-528
- GARDNER, G H, and others Studies on the pathological histology of experimental carbon tetrachloride poisoning, *Bull Johns Hopkins Hosp*, 1925, *xxvii*, 107-133
- HAMILTON, A Industrial poisons in the United States, 1925, Macmillan Co, New York, pp 441-442
- MINOT, A S, and CUTLER, J T Guanidine retention and calcium reserve as antagonistic factors in carbon tetrachloride and chloroform poisoning, *Jr Clin Invest*, 1928, *vi*, 369-402
- McMAHON, H E, and WEISS, S Carbon tetrachloride poisoning with macroscopic fat in pulmonary artery, *Am Jr Path*, 1929, *v*, 623-630
- LAPIDUS *Arch Hyg*, 1929, *cii*, 124 Quoted by Möller
- MAURO, G Intossicazione da tetracoloruro di carbonio, *Clin med ital*, 1930, *lxi*, 192-201
- LEHMANN, K B Führt die technische Verwendung von Tetrachlor-Kohlenstoff zu hygienischen Gefahren? *Zentralbl Gewerbehyg*, 1930, *xvii*, 123-133
- OKANO, M Studien über die Schädigung der Leberfunktion durch Tetrachlorkohlenstoff, *Jap Jr med Sci Trans IV Pharmacol*, 1930, *iv*, 167-188
- BECHER, E Über einen klinisch bemerkenswerten Fall von Vergiftung mit dem Fleckenwasser Spectrol, *München med Wchnschr*, 1930, *lxvii*, 890-891
- KIONKA, H Vergiftungsgefahr bei der Verwendung von Tetrachlorkohlenstoff zerstaubenden Feuerlöschapparaten, *München med Wchnschr*, 1931, *lxviii*, 2107-2108
- HEBERT, P, and PHELEBON Intoxication aigue (hepato-nephrite grave) par inhalation de tetrachlorure de carbone, influence de la chloruration sur les vomissements, *Rev gen d clin et d therap*, 1931, *xiv*, 327
- HENGGELE, A Ein erster Vergiftungsfall (Tetrachlorkohlenstoff-Vergiftung), *Schweiz med Wchnschr*, 1931, *lxi*, 223-224
- MINOT, A S Mechanism of hypoglycemia produced by guanidine and carbon tetrachloride poisoning and its relief by calcium medication, *Jr Pharmacol and Exper Therap*, 1931, *xliii*, 295-313
- BOLLMAN, J L, and MANN, F C Experimentally produced lesions of the liver, *ANN INT MED*, 1931, *v*, 699-712
- HAIGLER, F H Carbon tetrachloride poisoning, *U S Nav Med Bull*, 1932, *xxx*, 137-139
- LECORNU and PECKER Intoxication par le tetrachlorure de carbone, *Bruxelles med*, 1932, *xii*, 480-485
- PAGNIEZ, P, PLICHET, A, and KOANG, N K Un cas d'intoxication par le tetrachlorure de carbone, *Bull et mem Soc med d hôp d Par*, 1932, *lviii*, 1243-1246
- RICHER, C, JR, and COUDER, R Nephrite due au tetrachlorure de carbone, *Bull et mem Soc med d hôp d Par*, 1932, *lviii*, 1247-1248
- GAUTIER, C, CHATRON, M, and SEIDMANN, P Intoxication par le tetrachlorure de carbone, *Bull et mem Soc med d hôp d Par*, 1934, *xlx*, 1638-1650
- DALSGAARD-NIELSEN, T Case of carbon tetrachloride intoxication, *Ugesk f læger*, 1932, *xciv*, 969-970
- SEGITZ, A Zur Frage der "Vergiftungsgefahr bei der Verwendung von Tetrachlorkohlenstoff Zerstaubenden Feuerlöschapparaten," *Fabriksfeuerwehr*, 1932, *xxix*, 49-50
- CUTLER, J T The influence of diet on carbon tetrachloride in dogs, *Jr Pharmacol and Exper Therap*, 1932, *xlv*, 209-226
- LACQUET, A M Experimental pathology of liver, effects of carbon tetrachloride on normal and restored liver after partial hepatectomy, *Arch Path*, 1932 *xiv*, 164-176
- BUTSCH, W L Toxicity of carbon tetrachloride causing cirrhosis of the liver, *Jr Am Med Assoc*, 1932, *xcix*, 728-729

- MCGUIRE, L W Carbon tetrachloride poisoning, *Jr Am Med Assoc*, 1932, *xciv*, 988-989
- TANOHATA, K, and TAGAWA, D Histopathologische Untersuchungen über das Zentralnervensystem bei experimenteller Vergiftung mit Tetrachlorkohlenstoff, *Nagasaki Igakkaizasshi*, 1932, *v*, 1505-1506
- GALLORO, S Variazioni ematologiche nell'intossicazione da tetracoloro di carbonio e da tetracoloroetano, *Folia med*, 1932, *xviii*, 1616-1625
- MCCORD, C P Toxicity of carbon tetrachloride, *Indust Med*, 1932, *i*, 151-157
- TERASAKO, S Über die Reizwirkung des Tetrachlorkohlenstoffs auf die Leberfunktion, *Arb med Fak Okayama*, 1933, *iii*, 370
- DUVOIR, M, GUIBERT, and DESOILLE, H Les intoxications par le tetrachlorure de carbone, *Ann d med leg*, 1933 *xiii*, 533-543
- DE, A C Jaundice and acute mania following combined carbon tetrachloride and oil of chinopodium treatment for hookworm, *Indian Med Gaz*, 1933, *lxviii*, 150
- WIRTSCHAFER, Z T Toxic amblyopia and accompanying physiological disturbances in intoxication with carbon tetrachloride, *Am Jr Pub Health*, 1933, *xviii*, 1035-1038
- MÖLLER, K O Some cases of carbon tetrachloride poisoning in connection with dry shampooing and dry cleaning with survey of use and action of substance, *Jr Indust Hyg*, 1933, *vi*, 418-432
- MARTIN, E A propos d'un cas d'intoxication par le tetrachlorure de carbone, *Arch f Gewerbepath u Gewerbehyg* 1934, *v*, 208-209
- BIANCALANI, A Ricerche sperimentale sulla intossicazione Acuta e Cronica da Tetracoloro di Carbonio, *Arch Ital sci farmacol*, 1934, *iii*, 116
- HORROCKS, G E Carbon tetrachloride poisoning in ascariasis, *Mil Surg*, 1934, *lxxiv*, 246-247
- NELSON, R L Methylene blue in treatment of poisoning by carbon tetrachloride, preliminary report of three cases, *Minn Med*, 1934, *xvii*, 344
- POINDEXTER, C A, and GREENE, C H Toxic cirrhosis of liver, report of case due to long continued exposure to carbon tetrachloride, *Jr Am Med Assoc* 1934, *cii*, 2015-2017
- DAVIS, P A Carbon tetrachloride as an industrial hazard, *Jr Am Med Assoc*, 1934, *ciii*, 962-966

REPORT OF A CASE OF LEFT VENTRICULAR FAILURE WITH UNUSUAL ANATOMICAL CHANGES IN THE MYOCARDIUM *

By H ROESLER M D, and LOUIS A SOLOFF, M D, *Philadelphia, Pennsylvania*

THE recent publications of Weiss¹ and of White² have added much to the existing knowledge of the symptomatology of left ventricular failure. Our case is definitely an example of this condition and is the source of added information regarding the pathologic alterations and roentgenoscopic diagnosis.

A 37 year old white man, a clerk by occupation, was admitted to the hospital on February 11, 1933. He had had scarlet fever in childhood, and influenza in 1918. There was no history of rheumatism or syphilis, and a physical examination five years ago was said to be negative. One and one-half years ago he was rejected by an insurance company because of "kidney trouble." He was well until November 15, 1932 when he developed "grippe," but he continued at work until the onset of continuous and marked shortness of breath 10 days afterwards, together with general weakness, perspiration, and great palpitation on exertion. There was never any pain referable to the cardiovascular system. The shortness of breath was especially marked at night and was paroxysmal in character.

* Received for publication June 12, 1934.

From the Departments of Medicine, Roentgenology and Pathology, Temple University Hospital, Philadelphia, Pa.

On examination the patient suffered from marked dyspnea, orthopnea, and from frequent coughing. There was no cyanosis, no edema, and the liver was not enlarged. A gallop rhythm was visible and palpable. The heart was markedly enlarged to the left, the apex beat being indefinitely felt in the sixth intercostal space three cm to the left of the midclavicular line. On auscultation a systolic apical murmur and a well developed mid-diastolic gallop rhythm were heard all the way from the apex to the epigastric notch. The aortic second sound and the pulmonic second were equally intense. Small moist rales were present at both bases. The rhythm was regular with a rate of 110. The blood pressure at the time of admission was 220 systolic, and 120 diastolic. A few days later it was 164 systolic and 106 diastolic. The temperature was normal. The blood counts were normal, as were also the blood chemistry examinations. The urine showed a trace of albumin and occasionally a few hyaline casts. Examination of the kidney function revealed practically normal findings. The Wassermann-Kolmer and Kahn reactions were negative. The electrocardiogram showed regular sinus rhythm, a slight degree of left axis deviation, and the T-wave was isoelectric or diphasic in all three leads, con-

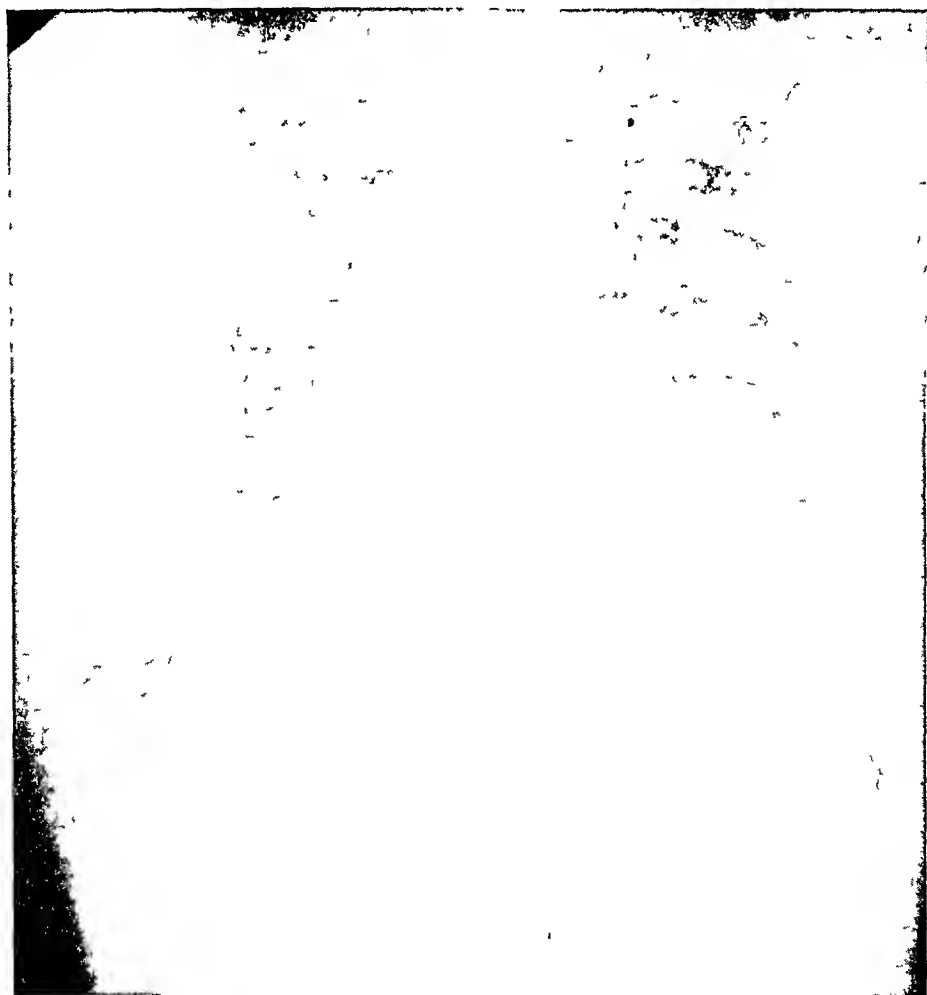


FIG 1 Roentgenological appearance of the chest at the time of the first examination of the patient, 7-13-33

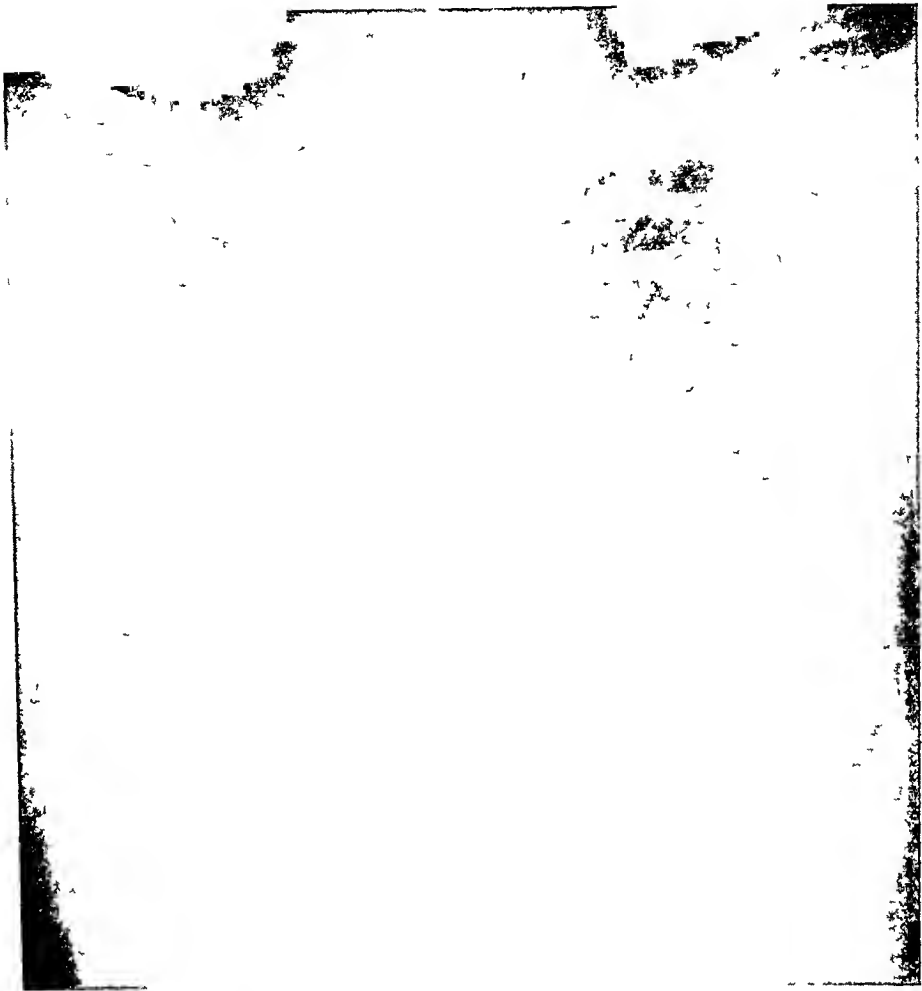


FIG 2 Roentgenological appearance of the chest when the patient showed very pronounced symptoms and signs of left ventricular failure, 3-7-33

stantly so upon repeated examinations. On roentgen-ray examination, a marked enlargement of the heart to the left and posteriorly, corresponding to the left ventricle, was made out. The left atrium showed no appreciable changes. There was a moderate amount of congestion in the lungs, especially in the central portions of the right lung. The amplitudes of pulsation as revealed by fluoroscopy were small.

On February 26 the patient developed an upper respiratory infection with fever. Shortly afterwards appeared cyanosis, hemoptysis with foamy blood, marked sweating, attacks of cardiac asthma at night, an increase in râles throughout the lungs, a marked accentuation of the pulmonic second sound, and some enlargement of the liver. The gallop rhythm became more marked. There was improvement, but after about two weeks another relapse, a new period of improvement and finally a continuous stage of heart failure with but little peripheral edema. During the last 15 days the maximum temperature was 101°F . Very marked congestive lung failure was present and a right pleural effusion was aspirated. During the course of the whole illness, there was a tendency for the blood pressure to fall, it reached 110 systolic and 90 diastolic a few days before death. The urea nitrogen exceeded the normal limit within the last

weeks and reached 29 mg per 100 c.c. The gallop rhythm was always present but almost completely disappeared several times following morphine injections. The electrocardiogram showed no fundamental changes. Repeated roentgen-ray films were made. The heart size showed no noticeable change. Remarkable were the changes in the degree of pulmonic congestion. A definite parallelism could be observed between decrease or increase of this and the clinical signs and symptoms of improvement or relapse. Only three pictures of the follow-up series are given (figures 1, 2, 3). It is noticeable that the central portion of the right lung appears of increased density, has a patchy, mottled, cloudy, confluent appearance which fades out hazily into the more peripheral portions. The corresponding changes in the left lung are almost completely hidden by the heart shadow, especially so because of the high position of the diaphragm. The periphery of the lung fields shows relatively good transparency.

During the course of the illness digitalis, strophanthin, salyrgan, metaphyllin and glucose were given.

The clinical diagnosis was Etiological—hypertensive cardiovascular disease,

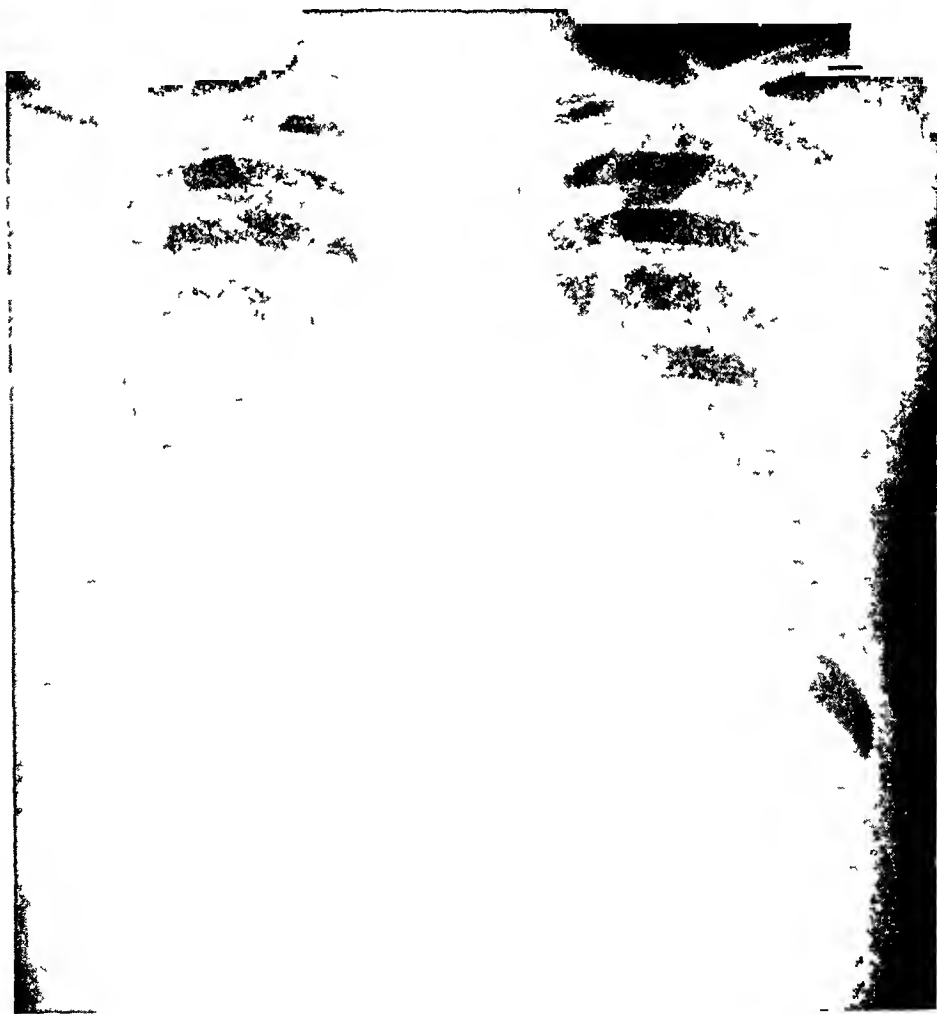


FIG 3 Roentgenological appearance of the chest about two weeks later, 3-24-33
Clinically improved

respiratory infection Anatomical—left ventricular hypertrophy and dilatation Coronary artery disease with possible occlusion of the left coronary orifice Bronchopneumonia Physiological—regular sinus rhythm, hypertension, left ventricular failure

Autopsy The patient died on April 28, 1933 Necropsy was performed three hours after death There was but a moderate edema of the lower extremities and also of the sacral region The abdominal cavity contained slightly more than two liters of light amber fluid The liver extended for eight cm below the right costal margin in the mid-clavicular line The upper half of the left pleural cavity was obliterated by firm fibrous adhesions The lower half was obliterated by fibrinous adhesions which were separated with some difficulty The entire right pleural cavity was obliterated by similar adhesions These extended over the diaphragmatic surface where on the inner third was located a small pocket containing about 60 c c of light amber fluid A large hemorrhagic infarct was present in the right upper lobe The right middle and lower lobes were completely consolidated The left lower lobe was almost completely solidified The spleen and liver were enlarged and the seat of marked chronic passive congestion The kidneys showed markedly arteriosclerotic and arteriolosclerotic changes The pericardium contained about 100 c c of amber fluid, and the lining was smooth and glistening The heart weighed 650 grams The epicardium was glistening and transparent except for a few fine shaggy threads of fibrin over an area measuring two cm on the middle of the anterior surface of the heart There was very little subepicardial fat The myocardium was moderately firm and dark red-brown The incised surface contained many long and broad gray streaks There were many circumscribed gray patches one to two mm in diameter in the left ventricle Only the mitral valve leaflets appeared altered and they were very slightly thickened The sinuses of Valsalva contained a few atheromatous plaques, more prominent in the left aortic sinus surrounding the orifice of the left coronary artery The descending and circumflex branches of the left coronary artery left the aortic sinus separately Their orifices were definitely constricted as compared to the lumina distal to them Dissection of these branches and of the right coronary artery revealed them to be patent, with a rare yellow fatty or atheromatous plaque The circumference of the right coronary artery was one cm, that of the descending branch of the left coronary 1.1 cm, and of the circumflex branch 0.9 cm The orifice of the descending branch was 0.6 cm in diameter, and of the circumflex branch 0.5 cm

Microscopic Description Representative sections of the left and right ventricle were studied They were stained with hematoxylin-eosin, Van Gieson, Verhoeff, and Gram stains The left ventricle presents a remarkable, striking appearance There are regions in all sections (figure 4) occupying approximately an entire low power field characterized by a complete disappearance of muscle bundles which has left a fine meshy reticular or lace-like structure Under higher power (figure 5) this is seen to be made up of fibrils containing no cytoplasm, or with clear unrecognizable cytoplasm, and a slight infiltration of macrophages, occasional lymphocytes, and rarely, polymorphonuclear leukocytes The cellular reaction in the interior of these lesions is unusually slight As the periphery of the lesions is approached, the various stages through which it must have gone are seen Many muscle fibers are seen lying free in the center of spaces lined by similar fibrillar lace-work Many of these fibers have no nuclei, others are completely hyalinized All have at least obscure striations More peripherally, hyalinization and acute degeneration of the muscle become prominent It is interesting to note, that as one examines from the fibrillar network outward toward the more normal appearing musculature, the cellular reaction becomes more intense and of a different character Within the fibrillar lesion the macrophage predominates, at the periphery of these lesions, the lymphocyte, and in the musculature itself, the neutrophilic polymorphonuclear leukocyte The muscle fibers are

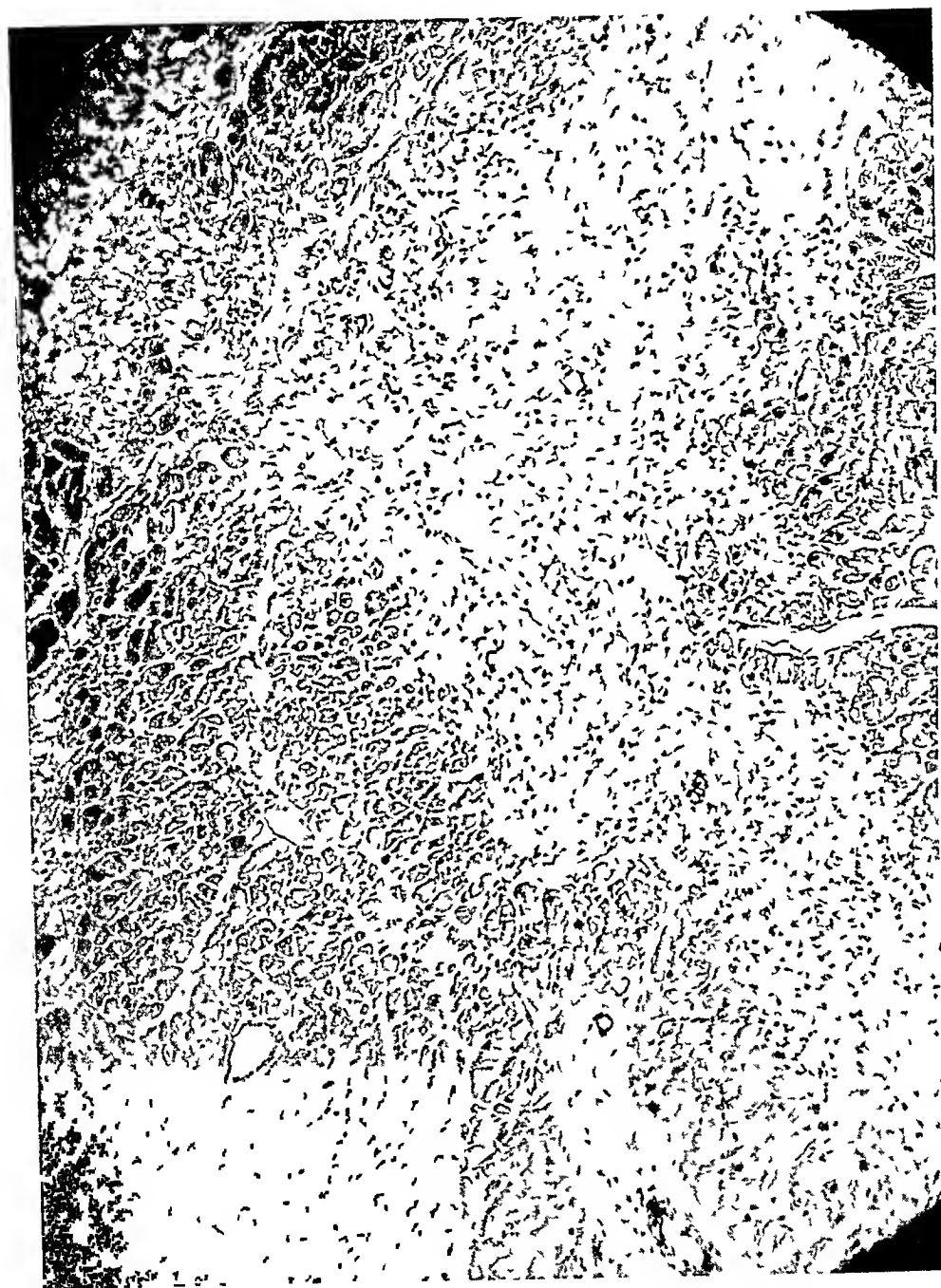


FIG 4 Left ventricular wall, low power, showing the characteristic distribution of the focal lesion.

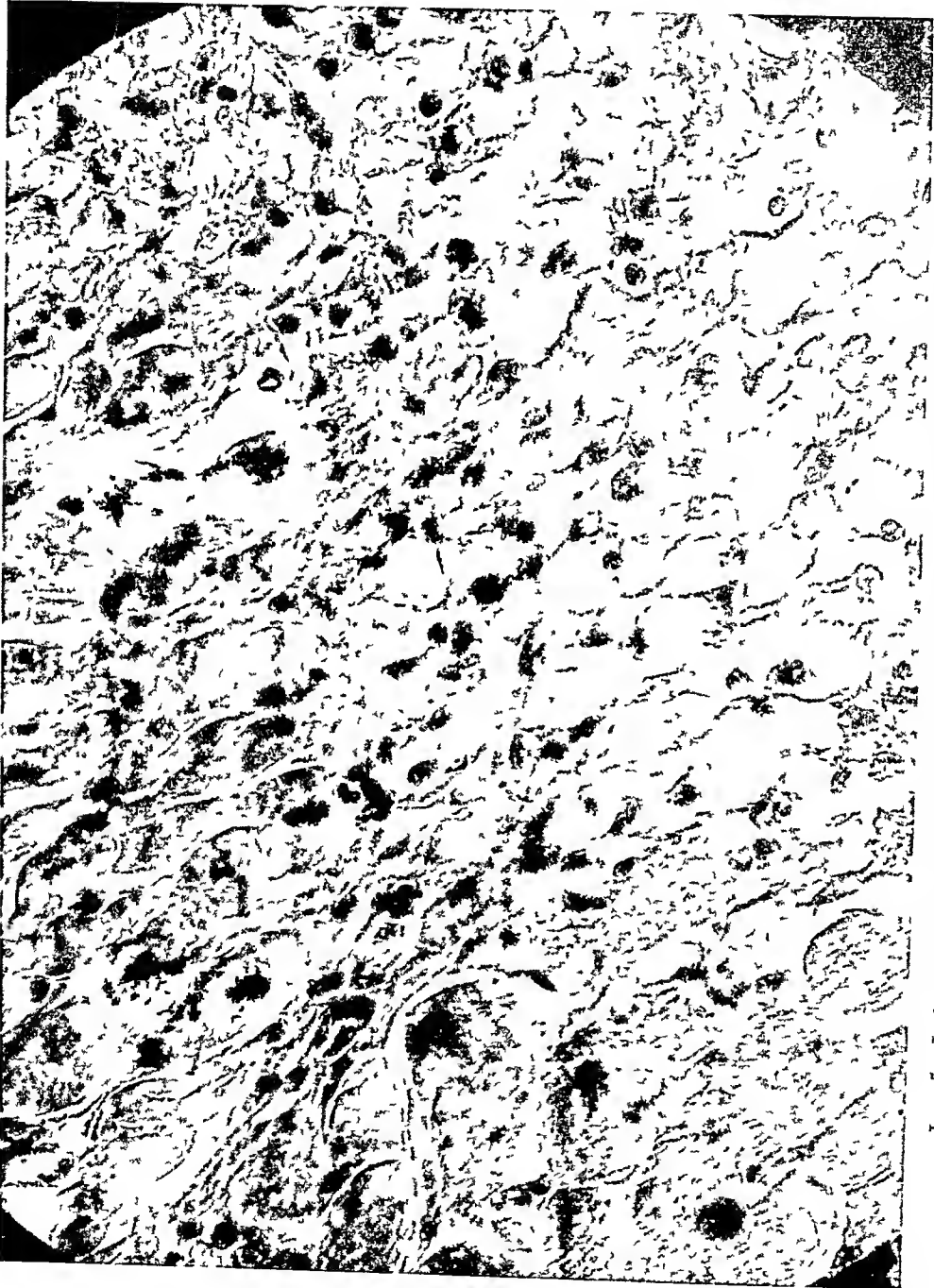


FIG 5 Left ventricular wall, high power, illustrating the complete loss of muscle fibers

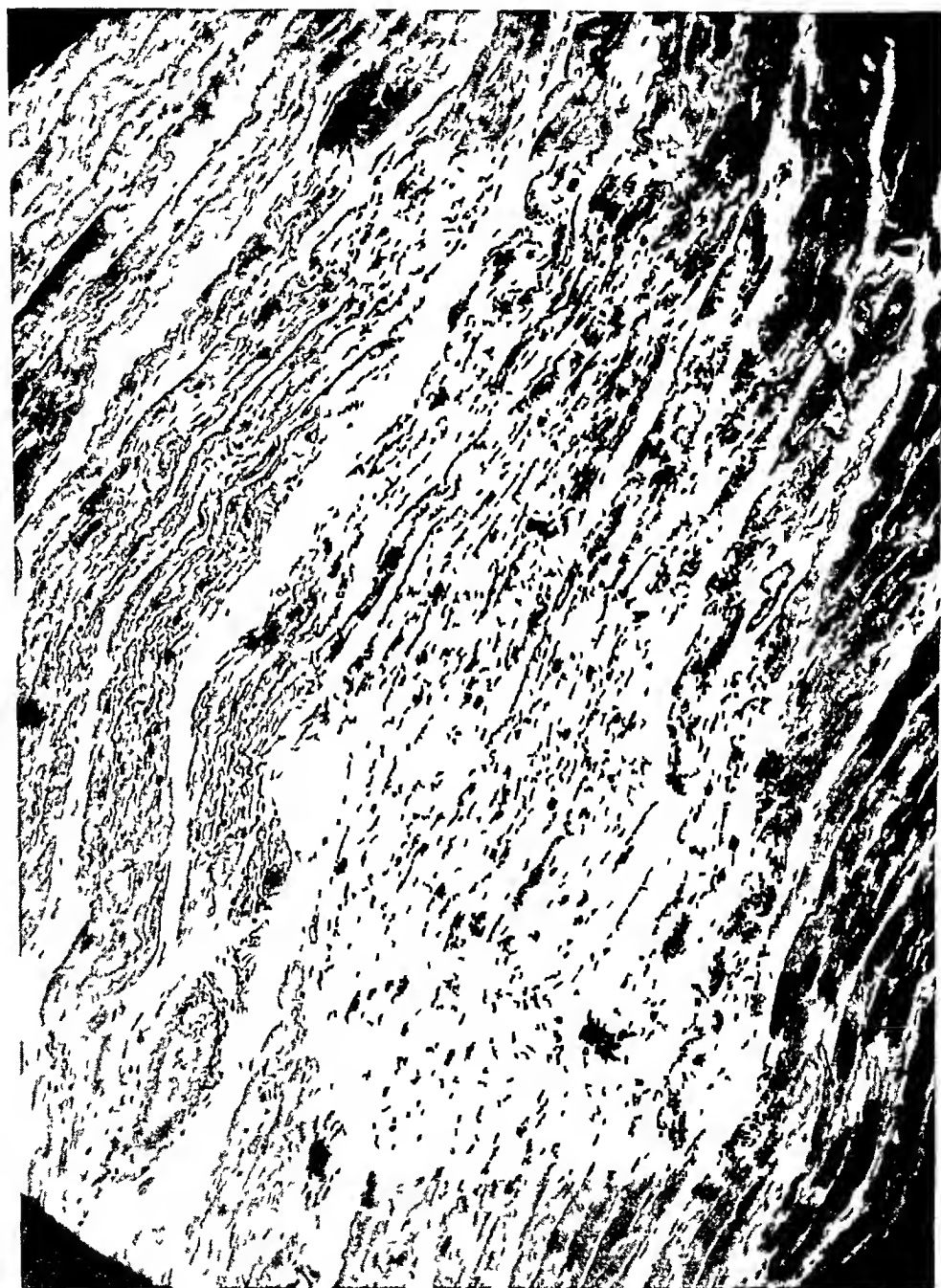


Fig 6 Right ventricular wall

distinctly larger than normal. The coronary vessels present nothing noteworthy except that they are dilated. It is probably significant that the focal fibrillary lesions are everywhere situated farthest from the coronary branches. The interstitial tissue of the hypertrophied musculature is increased. There are many regions of fibrosis and a mild exudate of polymorphonuclear leukocytes, plasma cells, lymphocytes and occasional macrophages. No bacteria were found. None of the sections of the right ventricle contains these lace-like lesions (figure 6). Except for a moderate hypertrophy of the musculature and perhaps a very slight fibrosis, the right ventricle presents nothing remarkable. On postmortem blood culture pneumococci (type III) were grown.

Pathologic Diagnosis Hypertrophy of the heart, particularly of the left ventricle. Acute degeneration of the myocardium. Fibrosis of myocardium. Subacute myocarditis with focal fibrillar fibrosis of left ventricle. Anomalous left circumflex artery. Mild arteriosclerosis of the coronary arteries and aortic sinuses. Stenosis of the orifices of the circumflex and descending branches of the left coronary artery. Mild fibrinous pericarditis. Mild atherosclerosis of the aorta. Fibrous adhesions, left upper lobe of lung. Pneumococcal pneumonia, right upper and middle lobe and left lower lobes. Encapsulated right diaphragmatic fluid. Subacute fibrinous pleuritis with granulation tissue. Arteriosclerosis and arteriolosclerosis of kidneys. Infectious hyperplasia with chronic passive congestion of spleen. Chronic passive congestion with mild central necrosis of liver. Ascites, dependent edema, icterus.

Two unusual features of this case might be emphasized: the unusual microscopic findings in the heart muscle, and the roentgenoscopic appearance of the lung fields.

Among the causes of this man's illness were hypertension, arteriosclerosis and arteriolosclerosis of the kidneys and myocardial hypertrophy with mild fibrosis. The respiratory infections, and especially the pneumococcal pneumonia, probably precipitated cardiac failure. The peculiar lesion limited to the left ventricle, appears unique. It resembles no other type of myocardial lesion with which we are familiar. That it is not infectious is shown by the absence of bacteria in the myocardium. We believe it is probably toxic. It is speculation to relate it to the upper respiratory infections at the beginning and during the course of the patient's sickness, or only to the pneumococcal pneumonia, or to both of them. We distinguish sharply the fibrosis due to the old hypertensive renal lesion and the subacute myocardial lesions. We have already remarked that the focal fibrillar lesions are situated at the greatest possible distance from the coronary branches. This suggests some relationship between the focal lesions and the blood supply. It is obviously not a question of sclerosis of the coronary branches, which was very slight in this case. It may, however, have something to do with the ability of the musculature to rid itself of its toxins which probably is more difficult in those regions where the blood supply is least. This may perhaps have some relationship to the unilateral character of the lesions,—its absence from the right ventricle being due to the thinness of its wall and perhaps better blood supply. The stenosis of the orifices of the left coronary branches may have some relation to the blood supply to the left ventricle, but we must admit that we have seen many cases of marked constriction of the coronary orifices and infection without similar lesions.

As to the roentgenologic aspect, various types of congestive lung failure have been observed. One type of congestive lung failure, as for instance seen in chronic mitral valvular disease, is fundamentally characterized by its diffuse distribution. Anatomically, the blood vessels as well as the lymphatics are di-

lated. A certain degree of induration, due to fibrosis, as well as of transudation is present, the latter especially around such foci of consolidation as old tubercles, scars, areas of atelectasis, and in the dependent, less aerated portions. In considering these main factors we observe in the film a general haziness with marked increase of the normal lung detail as well as a tendency to an appearance of diffuse fine mottling which occasionally is miliary in character. Quite different is the appearance in certain subacute or acute forms of disturbance of the hydrodynamic conditions in the lung, the most marked type being represented by the acute edema of the lung. Acute nephritis and failure in coronary arterial disease with hypertension are the best-known examples. From a roentgenologic viewpoint, the changes are less "vascular" in appearance. In other words, the appearance of the lungs in the present case cannot be accounted for on the basis of enlargement of blood vessel shadows as projected in longitudinal, oblique and transverse sections upon the film, with characteristic decrease of density and dimensions as the peripheral parts of the lung fields are approached. The usual appearance in this type of a case is a diffuse or mottled-patchy consolidation, the borders of which fade out rather rapidly into the surrounding lung area. Interstitial transudation, sometimes of a diffuse character, located around the central portion of the lungs, dominates the picture. As a matter of fact the apical and axillary portions remain remarkably free of these changes. Those lung portions where the active arterial filling is better, seem to be preferred. The right lung is usually more affected, which is to be compared with the generally greater tendency to right-sided pleural transudation. These changes can appear and disappear within a remarkably short time, as contrasted with the chronic changes in the lungs most typically observed in chronic mitral valvular lesions. They also may exist, in minor degrees, without giving characteristic auscultatory signs.

The observation of the roentgenologic appearance of the right lung field in this case could merely correspond to a pneumonic process. The histologic appearance, however, permitted us to estimate the duration of this process to be about two weeks and from a clinical viewpoint, fever was not present until 15 days before death occurred. The films showing the characteristic changes in question were taken seven weeks before death. Secondly, the change in the roentgenologic appearance was closely interrelated with the degree of cardiac decompensation. And finally, similar roentgen-ray pictures as observed in the course of cardiac decompensation, have been published by Zdansky, Chapman, Korns, Coe and Otell.

We have submitted the microscopic slides to Drs. C. Sternberg of the University of Vienna, W. Koch, of the University of Berlin, G. B. Gruber and W. Putschar, of the University of Göttingen, and wish here to express our thanks for their kind and valuable assistance.

REFERENCES

- 1 WEISS, S. Cardiac asthma (paroxysmal cardiac dyspnea) and syndrome of left ventricular failure, *Jr Am Med Assoc*, 1933, c, 1841-1846.
- 2 WHITE, P. D. Weakness and failure of left ventricle without failure of right ventricle, clinical recognition, *Jr Am Med Assoc*, 1933, c, 1993-1998.
- 3 ZDANSKY, E. Über das Röntgenbild des Lungenödems, gleichzeitig ein Beitrag zur Frage der Pathogenese des Lungenödems, *Röntgenpraxis*, 1933, v, 248-253.

- 4 CHAPMAN, J F Passive congestion of lungs in presence of coronary sclerosis, Radiology, 1931, *xvii*, 342-345
- 5 KORNs, H M Notes on heart failure, with report of case of pure left ventricular failure, Am Heart Jr, 1932, *viii*, 242-248
- 6 COE, F O, and OTELL, L S Acute pulmonary edema, Am Jr Roentgenol, 1932, *xxvii*, 101-102
- 7 ROUBIER, C, and PLAUCHU, M Sur certains aspects radiographiques de l'oedeme pulmonaire chez les cardiorenaux, Lyon med, 1933, *clii*, 137-145

EDITORIAL

*SURGICAL PROCEDURES IN ESSENTIAL HYPERTENSION**

The early work of Claude Bernard on the discovery of the vasomotor nerves was an event of tremendous importance. The application of this knowledge to problems in clinical medicine was delayed for half a century. The past decade has demonstrated in a most convincing fashion that, in man, removal of the sympathetic ganglions is followed by permanent vasodilatation of the arteries of the extremities. This has also been demonstrated in the experimental animal by exact quantitative methods. The thermistor-muhr method of Rein, thermometric readings in the deep and superficial tissues, have furnished controlled experimental evidence of this fact. Equally convincing have been the clinical observations in man. It may be stated at present, that with the complete removal of the appropriate sympathetic ganglions, permanent vasodilatation is produced in the lower extremities. In the upper extremities, sympathetic ganglionectomy does not affect prolonged vasodilatation in the same degree as it does in the lower extremities. The explanation of this difference is not clear. A logical result of this work was the attempt to apply operative procedures on the sympathetic nervous system in an attempt to control essential hypertension. The modern conception of the fundamental abnormality of this disease is that there is an inherited hypersensitivity of the vasomotor mechanism and that this defect is demonstrable in early years of life in children of hypertensive parents. This hypothesis carries with it the implication that the heightened responses in the blood pressures lead to hypertrophy of the *tunica muscularis* and increase in the blood pressure. Interruption of the vasomotor nerve supply of a large section of the arteriolar bed would theoretically modify or reduce these vasomotor reactions and decrease the blood pressure of subjects in whom the organic changes were not too advanced.

Among the various surgical procedures which are being tried are certain which involve the suprarenal glands. These operations are based on the hypothesis that increased amounts of epinephrine are concerned with the production and maintenance of essential hypertension. A tremendous amount of experimental evidence has given no basis for this conception. Physiologic studies seem to prove that the products of these glands are concerned with emergency functions and not with sustained effects. Denervation of the suprarenal glands has been carried out without evidence that the levels and responses in blood pressure are materially changed. It must be realized that complete denervation, as carried out on the suprarenal glands of man is most difficult and probably impossible. Partial resection of the suprarenal glands has been advocated. A critical survey of the effects of this operation would seem to indicate that the decrease in blood pressure may be secondary to a very definite systemic weakness, which may follow this

* Submitted for publication September 11, 1935

procedure. It is probable that the control of hypertension by operative measures on the suprarenal glands should not in our present state of knowledge be viewed too optimistically.

Operations on the sympathetic nervous system seem more logical and are engaging the attention of many workers. There are two types, resection of the splanchnic nerves either by supradiaphragmatic or infradiaphragmatic approach. The immediate and remote results of these operations are at present *subjudice*. Symptomatic improvement of the headaches, which are caused by the hypertension, and the general feeling of well-being have been noted. A significant decrease in the blood pressure when the patient is in the upright posture, and persistent lowering of levels and responses for long periods have not been conclusively demonstrated. This operation is carried out in two stages and entails a low risk. A more drastic operation is that of anterior rhizotomy, in which complete removal of the preganglionic sympathetic fibers below the fifth thoracic segment is accomplished by resection of the anterior roots from the sixth thoracic to the second lumbar nerves, inclusive. This procedure is followed by a loss of function of the sympathetic nerves below the diaphragm. All vasomotor fibers to the suprarenal glands, kidneys, abdominal vessels, and those to the lower extremities are interrupted. There is loss of sweating below the costal margin. Complete denervation of the splanchnic vessels is evinced by the sharp decrease in blood pressure that occurs when the patient is in the standing posture. The immediate effects within periods of one to three months after operation are dramatic. The value for the blood pressure decreases sharply to less than 100 mm. of mercury when the patient is in the standing posture. Symptoms are relieved and dilatation has been observed in the arterioles in the retina. The ultimate effects of this operation are yet to be determined. The applicability of this operation would, necessarily, be limited to the more severe forms of hypertension which affect the younger age groups, that is, those which affect patients who are less than forty-five or fifty years of age. The prognosis in these cases may be as grave as that of malignant growths. In this group, any procedure that would modify or delay the inevitable outcome is eminently justifiable. Careful selection of patients is important and those with renal, cardiac, or cerebral insufficiency should be excluded. The operation is one of some magnitude but no more so than many other operations that are attempted to control malignant disease. It has been carried out in two stages, thereby reducing the risk. There is some reason to hold an optimistic view of the ultimate value of such procedures in the treatment of hypertension. Careful and critical observations on the changes in blood pressure following operation are highly important. The evaluation of changes in the vasomotor function, as studied by the blood pressure, is at best difficult and beset with error. The supposed beneficial effects must be definite and prolonged. Studies must be carried out for long periods. The most significant single test for loss of the vasomotor splanchnic control is the postural decrease in blood pressure that occurs when the patient is in the upright posture.

REVIEWS

Clinical Laboratory Medicine and Diagnosis By R B H GRADWOHL, M D
1028 pages, 18 × 26 cm, 328 illustrations, 24 color plates First Edition C V
Mosby Co, St Louis 1935 Price, \$8 50

This work is a most admirable one in the field of diagnosis, and especially laboratory diagnosis. It covers the usual divisions of clinical pathology, as urinalysis, blood chemistry, hematology, gastric analysis, analysis of feces, sputum and punctate fluids. It devotes a chapter to pathology and exotic pathology, and one chapter each to special tests for rabies, allergy, pregnancy tests, chemical milk examination, mycological diagnosis, autogenous vaccines and semen appraisal. There is a chapter each on bacteriology, serology, basal metabolic determinations, postmortem examination, tissue cutting and staining, preparation of museum specimens, and on toxicological technique.

The author draws from an extremely wide personal experience, both from his own laboratories and from the laboratories of others. According to the record, he began the study of pathology some 35 years ago. He studied abroad under such renowned masters as Virchow and Langerhans of Germany and Chiari of Austria, and one can feel the influence of the Continental schools, chiefly the Germanic, woven into the work. An extremely large share of the references are to the German medical literature, and some of the illustrations are reproductions of German originals.

Some of the 18 chapters are rather abbreviated, as for instance the chapter on sputum which is condensed into seven pages, and the chapter on gastric analysis which is only 21 pages in length. Other chapters, however, cover their subject rather exhaustively, as for instance the chapters devoted to hematology and bacteriology and bacteriological applications to clinical diagnosis. Both of these deserve special mention because of outstanding merit, and together they occupy 336 pages. Any disappointment over the brevity of certain sections or whole chapters is compensated by the adequacy of the treatment of major topics.

The 352 illustrations and plates aid greatly in clarifying the text. Of these about 250 are original illustrations and color plates and about 102 are reproductions from other works and authors. The 24 color plates are well done.

One may say with justice that this book represents the life work of its author in a large and varied medical field. It is much more pretentious than some of the recent short-cut works in clinical pathology. It combines clinical pathology, pathology, histology, and postmortem study with bedside diagnosis. And while some of the sections are somewhat outdated by more recent work, it may be considered an extremely valuable book which deserves a prominent place in the general library or for ready reference on the laboratory desk.

S L J

Blood Groups and Blood Transfusion By ALEXANDER S WIENER, A B, M D
xiv + 220 pages, 17 × 26 cm Charles C Thomas, Baltimore 1935 Price,
\$4 00

Few will question the statement that this book will immediately become the acknowledged English text on Blood Groups. Unlike many who may be complete masters of a complex subject but are singularly inept in teaching first principles, Wiener has happily achieved a treatise which is primer-like in its exposition of material to the beginner. Yet the student will find, in addition, all the wealth of investigative work leading up to our present knowledge of this intricate subject. After a thorough review of the four blood groups, the subgroups of group A and AB and

the agglutinogens M and N of Landsteiner and Levine are presented in great detail and with remarkable clarity. The latter half of the book deals largely with investigations into the genetic, biometric and anthropological aspects of the blood groups, and finally there is a very lucid exposition of their medico-legal applications,—in which latter field, of course, Wiener is an acknowledged master.

The chapters on Blood Transfusion are not exhaustive but, on the whole, are adequate. The last few years have seen a very marked decrease in the incidence of post-transfusion reactions of the so-called "foreign body" type. The recognition that they can be practically eliminated by proper routine cleansing of apparatus and preparation of solutions is now widespread. These facts, while not omitted, have hardly been sufficiently stressed. Some of the newer and popular direct transfusion apparatuses have been omitted.

The general excellence of the book, however, overshadows any minor faults and it may truthfully be said that to the student of blood groups this book is unique and invaluable.

H R P

The Story of Medicine in the Middle Ages. By DAVID RIESMAN, M.D., Sc.D., F.A.C.P., Professor of the History of Medicine and Professor Emeritus of Clinical Medicine, University of Pennsylvania, Member, History of Science Society and Medieval Academy of America. xii + 402 pages, 79 illustrations. Paul B. Hoeber, Inc., New York. 1935. Price, \$5.00.

It required courage as well as insight and industry to write *The Story of Medicine in the Middle Ages*. Most medical historians have passed lightly over the period which has disparagingly been called the Dark Ages, and its achievements have been overlooked or minimized. Then, too, the historian was under necessity of placing temporal limits upon the period with which he dealt. For the beginning of the Middle Ages, dates as varied as that of the birth of Christ and of the crowning of Charlemagne, 800 years later, have been proposed. As to the termination of the period, the arresting suggestion that we may still be in the Middle Ages is not without some basis, although doubtless it will be accepted with the tolerant chuckle with which it was given. For each of many recent generations the "Middle Ages" has signified an indefinite period somewhat remotely antedating the epoch of its own naively egotistical superiority. Dr. Riesman follows most modern historians in assuming that the Middle Ages ended several centuries ago.

Not once does *The Story of Medicine in the Middle Ages* become a tiresome chronicle. After a number of chapters dealing with the Greek inheritance, the monastic influence and the part played by Arabian and Jewish physicians, the schools of medical thought are discussed. Then is described the rise of the universities, perhaps the most important factor in the development of modern culture. Of these there were at least eighty, but Montpellier, Bologna, Padua, Paris and Oxford and Cambridge were of special importance in medical matters. These provide chapter headings. The growth of the divisions of medical thought—atomy, surgery and sanitation—is traced and the extraordinary epidemics, some of which are even today imperfectly identified, are described. The evidence for and against the American origin of syphilis is assembled and condensed. While definite decision is withheld, the author may be suspected of inclining to the anti-American opinion. The free use of quotations from original sources and abundant references in footnotes make this a well-documented text for the student of medical history, but its interesting material and lively style recommend it also to the general reader.

Dr. Riesman concludes that the Middle Ages possessed three outstanding advantages that no longer obtain: one dominant religion, one social system, one universal language. Two other characteristics, of lesser importance, were the distinction

conferred by scholarship and the abundant opportunity for poor scholars to achieve an education "The greatest difference between modern times and the Middle Ages, in medicine as well as in all sciences, is the objective, the experimental method"

C V W

Amebiasis and Amebic Dysentery By CHARLES F CRAIG, M D 315 pages, 17 X 25.5 cm First Edition Charles C Thomas, Springfield, Ill 1934 Price, \$5.00

This is a complete treatment of the subject of amebiasis and amebic dysentery, by a well known authority in this field. The 12 chapters cover the etiology, epidemiology, pathology, symptomatology, complications and sequelae, diagnosis, complement-fixation test, prognosis and prophylaxis, and finally the treatment of the disease. Each one of these 12 chapters concludes with an extensive bibliography.

This book was most timely, appearing as it did very shortly after the outbreak of amebic dysentery following the Chicago World Fair. Its lasting usefulness, however, is well assured, for according to the statistical figures, contained in the chapter on epidemiology, between 5 and 10 per cent of the population of the United States harbor the ameba at some time in their life. If these figures are accepted it would mean that between six and twelve million people in this country are potential amebic patients.

Dr Craig has written a valuable monograph on an important subject. It will be useful not only to the parasitologist and the clinical pathologist but also to the internist. There is a very adequate discussion of the symptomatology and of the complications of amebic dysentery and a conservative evaluation of the many types of therapy which have been proposed. The author's views as to the clinical effects of amebiasis without outspoken dysentery are of great interest.

S L J

Physical Diagnosis By WARREN P ELMER, B S, M D, and W D ROSE, M D 919 pages, 15.5 X 23.5 cm C V Mosby Co, St Louis 1935

The seventh edition of Elmer and Rose's "Physical Diagnosis" constitutes a further improvement of this excellent textbook. The excellent chapters on clinical anatomy and physiology are very clearly written and splendidly illustrated. The larger part of the following text is given over to physical diagnosis as applied to the respiratory and circulatory systems. These are very adequately dealt with. The essentials of physical diagnosis in other regions of the body than the chest are also covered. Laboratory methods of diagnosis are not included.

The book is well bound, the type is large, the illustrations are well chosen. It deserves widespread use.

T C W

COLLEGE NEWS NOTES

Dr H R M Landis (Fellow), Philadelphia, is Associate Director in charge of the clinical and sociological departments of the Henry Phipps Institute of the University of Pennsylvania

Dr George W Grier (Fellow), Pittsburgh, was installed as President of the American Radium Society at its annual meeting in Atlantic City

Dr Olin S Allen (Fellow), Wilmington, Del, is a member of the Medical Council of Delaware

Dr Chester M Jones (Fellow), Boston, and Dr Russell S Boles (Fellow), Philadelphia, became President-Elect and Secretary, respectively, of the American Gastro-Enterological Association at its last annual meeting

Dr Edward S Sledge (Fellow), Mobile, Ala, has been made a Vice-President of the Chattahoochee Valley Medical Association

Dr Francis W Heagey (Fellow), Omaha, Nebr, has been elected President of the Nebraska Tuberculosis Association

Dr Kenneth M Lynch (Fellow), Charleston, S C, has been appointed to the State Board of Health, succeeding Dr Robert Wilson (Fellow), resigned

Dr David W Carter (Fellow) and Dr Homer Donald (Fellow), both of Dallas, Tex, have been made President and Treasurer, respectively, of the Dallas Southern Clinical Society for the ensuing year

Dr George Fordham (Associate), Powellton, W Va, has been elected President of the West Virginia Society of Industrial Physicians and Surgeons

Dr Walter C Swann (Fellow), Huntington, Dr A H Stevens (Fellow), Fairmont, and Dr R J Condry (Fellow), Elkins, have been made President, Vice-President and Secretary, respectively, of the West Virginia Heart Association

Dr Fritz B Talbot (Fellow), Boston, has been elected President of the American Pediatric Society for the ensuing year

Dr James W Hunter (Fellow) and Dr Walter B Martin (Fellow), both of Norfolk, have been installed as President and President-Elect, respectively, of the Norfolk County Medical Society

Dr James J Waring (Fellow), Denver, Colo, has been elected President of the National Tuberculosis Association

Dr Charles J Bloom (Fellow), New Orleans, La, has been elected President of the Louisiana State Pediatric Society

Dr James B Collip (Fellow), Montreal, Que, Dr Elliott P Joslin (Fellow), Boston, and Dr O H Perry Pepper (Fellow), Philadelphia, hold membership on the Board of six scientists appointed as an advisory council to the George S Cox Medical Research Institute of the University of Pennsylvania. The Institute was founded in 1932 with a fund provided under the will of the late Mr Cox, a Philadelphia banker and manufacturer. The council will hold annual meetings to receive reports, review work of the Institute, which is devoted to the study of diabetes, and to consult with the staff on further investigations

Dr John S Hibben (Associate), Pasadena, Calif, was installed as President of the American Congress of Physical Therapy at its meeting in Kansas City, September 9 to 12

Dr Isaac Hall Manning (Fellow), formerly Dean of the University of North Carolina School of Medicine, is President of the recently organized Hospital Savings Association of North Carolina. Among the directors are Dr Paul P McCain (Fellow), Sanatorium, President of the Medical Society of North Carolina, and Dr Louis B McBrayer (Fellow), Southern Pines, Secretary of the Medical Society of North Carolina

Dr Guy H Turrell (Fellow), Smithtown Branch, L I, N Y, has been elected Secretary of the New York State Sanitary Officers' Association

OBITUARIES

DR HARRY WINFRED GOODALL

Dr Harry Winfred Goodall died April 17, 1935, at Boston, Massachusetts, in his fifty-eighth year

Born in Wells, Maine, the son of George B and Isabel M (Norton) Goodall, he attended the Berwick Academy and received his A B at Dartmouth College where he was awarded the Grimes Prize and became a member of Kappa Kappa Kappa. In 1902 he was graduated *summa cum laude* from the Harvard Medical School. Following a two year internship at the Massachusetts General Hospital, a service at the Boston Lying-In Hospital, an assistant residency at the Massachusetts General, he began in 1904 the practice of medicine. In 1908 Dr Goodall pursued advance studies at the University of Tubigen in Germany.

Dr Goodall was at one time lecturer on digestive diseases at the Dartmouth Medical School as well as instructor in chemistry at the Harvard Medical School. He served during the World War both in this country, at Camp Greene, North Carolina, and Camp Wheeler, Georgia, and overseas as commanding officer of the gas hospital at Toul, France, and as chief of the medical service at Base Hospital No 51. On August 26, 1921, Dr Goodall was awarded the Distinguished Service Cross for "exceptionally meritorious and distinguished services in the performance of duties of great responsibility as Lieutenant Colonel, Medical Corps, U S A, in command of the gas hospital of the Justice Hospital Group in the American Expeditionary Forces during the World War."

Dr Goodall collaborated with Dr Otto Folin on "Saccharin and the Health of Man," with Dr E P Joslin on "The Treatment of Diabetes Mellitus" and with Dr Francis G Bennett on "A Study of Prolonged Fasting" and "The War Diary of a Medical Officer," and by himself wrote authoritative works on thoracic stomach.

Dr Goodall served on the staff of the Boston Dispensary, the New England Baptist Hospital, the New England Deaconess and the Palmer Memorial. He was a member of the Council of the Massachusetts Medical Society, a Fellow of the American College of Physicians (1931), a member of the American Medical Association, and belonged to the Masons, the Military Order of the World War, the Harvard Club of Boston, and the Square and Compass Club.

Dr Goodall was married in 1925 to Emma Claflin Pierce of Boston who died in 1932. He leaves two brothers, George E Goodall of Wells, Maine, and Frank R Goodall of Exeter, New Hampshire.

WILLIAM B BREED, M D , F A C P ,
Governor for Massachusetts

DR FREDERICK EPPLEN

Dr Frederick Epplen, Seattle, died suddenly in an attack of angina pectoris May 25, 1935, after an illness of over four years

Dr Epplen was born April 11, 1880, in Dennjacht, Germany. He began his medical education at the University of Nebraska and was graduated from Rush Medical College in 1906. After an internship in Cook County Hospital he practiced in Miles City, Montana, and in St Joe, Idaho. He then took postgraduate work in Vienna and located in Spokane for the practice of internal medicine. In 1927 he moved to Seattle and practiced there until disabled by illness in 1931.

During his years in Spokane and in Seattle he was an outstanding figure in the profession, of more than local prominence. He was always a deep student, and it was his constant effort to improve the plan of medical practice both in his own office and in the profession at large. He was always active in the various medical societies to which he belonged. The encouragement, advice, and friendly criticism which he was always ready to give will long be remembered by those who were fortunate enough to be associated with him.

He gave a great deal of time and work to the Pacific Northwest Medical Association, an organization for postgraduate instruction, and its success in the early years was due largely to his guidance. He was one of the organizers and the first president of the North Pacific Society of Internal Medicine, and lived to see it become active and vigorous, to his great happiness. He prized his membership in the Pacific Interurban Club, and made every effort to attend its meetings, even during his illness. The College has suffered a great loss in his death.

During the many years when he was Governor for Washington of the American College of Physicians, it seemed always foremost in his thoughts, and he worked constantly for the improvement of the College. He attended the Philadelphia Session in April of this year, knowing well before he went that his heart was in no condition for such a trip. His love for the associations and friendships of the College urged him on to attend this last meeting, even though it would be likely to hasten his death.

He is survived by his widow, Mrs Ruth Merrill Epplen, a daughter, Miss Dorothy Epplen, of Claremont, Calif., and a brother, Carl Epplen in South Dakota.

CHARLES E. WATTS, M.D., F.A.C.P.,
Governor for Washington

DR LOUIS F JERMAIN

Dr Louis F Jermain, Dean Emeritus of the Marquette University School of Medicine, Milwaukee, Wisconsin, died on July 24, 1935, following a long illness.

Dr Jermain was born in Manitowoc County, Wisconsin, in 1867. His preliminary education was obtained in local schools, following which he taught in a country school for seven years. At the age of twenty-four years he entered Northwestern University Medical School, from which he was graduated in 1894.

Upon his graduation Dr Jermain came to Milwaukee where he joined the faculty of the old Wisconsin College of Physicians and Surgeons. He later became a member of the faculty of Marquette College and was largely responsible for the merging of that College with the Wisconsin College of Physicians and Surgeons in 1913, when he was appointed Dean of the Medical School, which office he held until the year 1926.

Dr Jermain was assistant City Health Commissioner from 1908 to 1910. He became a member of The Medical Society of Milwaukee County on February 14, 1902, and in 1910 he was elected President. In 1916 he became President of the State Medical Society of Wisconsin. Upon the recommendation of Archbishop Sebastian G. Messmer, Dr Jermain was made a Knight of the Order of St. Gregory the Great by Pope Pius XI in 1924.

Because of his contribution to medicine and long activity in the interests of the medical profession, Dr Jermain was unanimously elected Honorary Member of The Medical Society of Milwaukee County on March 8, 1935. Dr Jermain became a Fellow of the American College of Physicians during 1920.

ROCK SLEYSER, M D , F A C P ,
Governor for Wisconsin

DR. FREDERICK RIGBY BARNES

Dr Frederick Rigby Barnes (Fellow), born in Philadelphia, Pa., August 12, 1890, died July 18, 1935, in the Union Hospital, Fall River, Mass. He had been in poor health for two years, as a result of a staphylococcal infection of the blood stream following accidental puncture of a vein on the back of his hand with an infected hypodermic needle while treating a patient. During the last few months it appeared he would recover, and he had resumed practice.

Dr Barnes attended Bucknell University and later obtained his medical degree at the University of Pennsylvania School of Medicine, graduating in 1913. He interned at the Chestnut Hill Hospital and then spent two years as resident physician and surgeon at the German (now the Lankenau) Hospital in Philadelphia.

In 1917 he went to Fall River, but early in the World War enlisted, attained the rank of captain, and served with the Pennsylvania (Philadelphia) Hospital unit at an English base in France. Dr Barnes served as associate medical director for his district for eight years and in 1927 was appointed medical examiner by Governor Alvan T. Fuller. He was chief of the medical service at the Truesdale Hospital.

Dr Barnes became a Fellow of the American College of Physicians during 1930, and promptly thereafter became a Life Member. He was the author of a number of published articles, and a man of wide reputation in his part of the country. He was a member of the Phi Gamma Delta and the Phi Alpha Sigma Fraternities, a past Secretary and past President of the Fall River Medical Society, a member and councillor of the Massachusetts Medical Society, a member of the Massachusetts Medico-Legal Society, and a Fellow of the American Medical Association.

DR JOHN MASON MORRIS

Dr John Mason Morris (Fellow), Louisville, Ky, was born April 25, 1861, at Sulphur, Ky, and died July 18, 1935, Louisville, Ky, at the age of seventy-four.

Dr Morris was an outstanding example of a family physician and retained the fine traditions of the old time medical profession. He always had the interest of his patients at heart, regardless of their ability to remunerate him for his services. As a consequence, he has left behind a host of patients to mourn his death, as well as members of the medical profession of Louisville who respected him for his kindness of heart, his devotion to his profession and his loyalty to his friends.

He was a member of the American Medical Association, the Southern Medical Association, the Kentucky State Medical Association and its component societies, and he became a Fellow of the American College of Physicians in 1927.

C W DOWDEN, M D , F A C P ,
Governor for Kentucky

DR THURSTON HOPKINS DEXTER

Dr Thurston Hopkins Dexter (Fellow), Brooklyn, N Y, died June 24, 1935, at the age of fifty-eight years. Dr Dexter was born and educated in Brooklyn. He graduated from the Long Island College Hospital in 1901. His practice was devoted to pathology and bacteriology. He was pathologist and bacteriologist at the Methodist Episcopal Hospital, 1905-14, Williamsburg Hospital, 1907-10, Coney Island Hospital, 1908-11, Bushwick Hospital, 1909-15, Lutheran Hospital, 1909-17. At the time of his death he was chief pathologist at the Wyckoff Heights Hospital and the Swedish Hospital.

During the World War Dr Dexter held the rank of Major and was in command of field hospitals of the 301st Sanitary Train, and later the 4th Corps Sanitary Train, serving in the Meuse-Argonne sector. After the war he was for seven years regimental surgeon of the 101st Cavalry, National Guard, and held the rank of lieutenant colonel in the Medical Reserve Corps.

He was the author of several published articles, a member of his county and state medical societies, a Fellow of the American Medical Association and ex-President of the Brooklyn Pathological Society, Brooklyn Hospital Club and Long Island College Alumni Association. He was also a member of the Associated Physicians of Long Island and the Association of Military Surgeons. He became a Fellow of the American College of Physicians during 1929. His burial took place at Arlington Cemetery, Washington.

DR FRANKLIN WELKER

Dr Franklin Welker (Fellow), New York, N. Y., died July 17, 1935, at his summer home in Highland, N. Y., of heart disease, at the age of sixty-eight years.

Dr Welker was born at Attica, N. Y., July 20, 1867. He attended the University of Rochester, from which he received the degree of A. B., and then pursued his medical education at the University of Pennsylvania, graduating in 1894. He spent his internship at the Kings County Hospital, Brooklyn. For many years he was attending physician and medical director of the Lutheran Hospital of Manhattan, which appointment he held at the time of his death. He was President of the Medical Society of the County of New York, and a member of the New York Academy of Medicine, the Medical Association of Greater New York, the Harlem Medical Association, the Washington Heights Medical Society, the West Side Clinical Society, the National Tuberculosis Association and a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians on December 1, 1923.

Dr Welker was especially known as a physician who sought to uphold the position of the general practitioner in the medical profession. He was opposed to governmental encroachment in the field of medicine in competition with both private hospitals and individual physicians. He did not believe in compulsory health insurance plans, which would place the medical profession under the control of laymen and politicians. While he admitted the need for governmental hospitals, he felt they should not be permitted to submerge private institutions. At his induction as President of his county society, last January, he said in part, concerning compulsory insurance:

Most, if not all, of the abuses connected with medical service in workmen's compensation have grown out of the suppression of the free choice of physicians, and investing the insurance carriers and employers with control over treatment. Business men chose the doctor, and their concern is cheap care, rather than good care. Under their egis commercial clinics have sprung up that harbor every evil that can come into healing—inefficiency, unnecessary prolongation of treatment, rebating, "lifting" of cases and padding of bills.

Dr Welker was always a student. He was quiet and of even disposition, and was especially characterized by his thoughtfulness of others.

Surviving him are his wife, Mrs Louise A Welker and two daughters, Mrs E L Rohdenburg and Miss Marian Welker

DR FRANCIS W HEAGEY

Dr Francis W Heagey (Fellow), Omaha, Nebr, died August 23, 1935, of an embolism, one week after an appendectomy, aged fifty-one years

Dr Heagey was born at Bareville, Pa, attended Princeton University for his academic training, and graduated from Columbia University College of Physicians and Surgeons in 1912 with the degree of Doctor of Medicine. He practiced in New York City until 1916 when he went to Omaha to engage in practice and to become Instructor in Medicine at Creighton University School of Medicine. At the time of his death, he was Associate Professor of Medicine at Creighton University School of Medicine, Attending Physician to Creighton Memorial, St Joseph's Hospital. He was a member of the Douglas County Medical Society, the Nebraska State Medical Association, a Fellow of the American Medical Association, and until recently president of the Nebraska State Tuberculosis Association.

Dr Heagey was deeply interested in welfare work, a member of the State Emergency Relief Committee, and sometime president of the Omaha Child Welfare League and the Omaha Council of Social Agencies. He had contributed voluminously to medical literature, and was recognized as a man of distinctive worth to his community. He became a Fellow of the American College of Physicians in 1922.

DR JESSIE WORTHY LEA

Dr Jessie Worthy Lea (Fellow) of Jackson, Louisiana, died July 9, 1935, of coronary occlusion, aged 66.

Dr Lea received his M D degree from Tulane University, Medical Department, in 1891. He was a member of the East and West Feliciana Parish Medical Society, Louisiana State Medical Society, the American Medical Association and in 1929 he was made a Fellow of the American College of Physicians.

He served as president of his local medical society, president and counselor of the Sixth District Medical Society. For eight years he served on the staff of the East Louisiana State Hospital, and also served as a member of the board of administrators of this institution.

Dr Lea was a delightful personality who was loved and appreciated by his many friends. He is survived by his wife, Miss Grace M. Lea.

J. E. KNIGHTON, F. A. C. P.,
Governor for Louisiana

ANNALS OF INTERNAL MEDICINE

VOLUME 9

NOVEMBER, 1935

NUMBER 5

THE MECHANISMS OF HEALING IN COLLAPSE THERAPY *

By MAX PINNER, M D , F A C P , *Tucson, Arizona*

THE results of collapse therapy, despite their spectacular improvement during the last decade, are often inconstant, unpredictable and disappointing. As culled from the literature the reasons for success or failure are manifold and often contradictory. On the other hand, a large number of clinical, pathological and experimental studies provides a sufficient basis for a discussion of the factors that play a beneficial or disturbing rôle in collapse therapy. While many single phases have been studied carefully, I failed to find in the literature a comprehensive discussion of the problem as a whole. A clear conception of the physiology of pulmonary collapse should obviously be the basis for correct therapeutic indications.

In this brief review it is impossible to discuss, with proper bibliographical documentation, the many divergent opinions on the subject. This will appear in a more extensive later publication. Within the time allotted for this presentation it is possible only to state briefly, and in rather categorical manner, what, on the basis of available knowledge, seems to be a justified idea of the mechanism of healing in pulmonary collapse. This is offered as a temporary working hypothesis which is necessarily far from complete. However, it has at least the virtue of clearing the field of a number of customary misconceptions.

Pulmonary collapse represents a reduced total volume of the lung. This may be induced by introducing foreign substances into the thoracic cavity (air, oil, paraffin, etc.), by paralyzing or cutting respiratory muscles (diaphragm, scaleni, intercostals), or by reducing the size of the bony thoracic cage.

When pulmonary collapse is established a number of compensatory mechanisms come into play, some of them operate immediately after collapse, others develop gradually and slowly. Many apparent contradictions in the literature are due to the fact that observations on brief acute experi-

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

From the Laboratories of the Desert Sanatorium and Institute of Research, Tucson, Arizona.

ments have been applied to therapeutic collapse which is always a chronic condition

Another reason for confusion is the use of different species of experimental animals. Some species (guinea pigs, dogs) have a permeable mediastinum, so that any collapse measure (and particularly pneumothorax) instituted on one side causes bilateral collapse automatically, while other animals (rabbits, goats) have, like men, an impermeable mediastinum which, however, varies greatly in rigidity.

In the early era of pneumothorax therapy the aim was to immobilize the lung by superatmospheric intrapleural pressures. Later on it was found that subatmospheric intrapleural pressures yielded, in the majority of patients, equally good and better results than high positive pressures. At present, it ought to be, and probably is, common practice to maintain subatmospheric pressures unless stiff-walled cavities indicate the necessity of positive pressures for actual compression. But the logical explanation of the action of positive-pressure pneumothorax has been carried over insidiously and unjustifiably to subatmospheric pneumothorax and other collapse measures. This is a typical example of the lag that exists so often between practice and theory.

The following brief and necessarily incomplete list of the factors held responsible for enhancing healing under pulmonary collapse will indicate the chaotic state of the problem: (1) Rest of the collapsed lung, or part of it, (2) Elastic relaxation of pulmonary tissue, (3) Alteration of the circulation of the blood in the lung—hyperemia, blood stasis, relative anemia, (4) Alteration in the gaseous metabolism of the lung—anoxia, increase in carbon dioxide, (5) Stasis of lymph, (6) Atelectasis—bronchial obstruction, (7) Cessation of spread in collapsed lung.

(1) Rest of Collapsed Lung The respiratory motions of the lung are solely activated by the motion of the chest-wall (including the diaphragm). This is equally true for a normally expanded as well as for a collapsed lung. As long as any of the respiratory muscles perform their normal function so long is the lung ventilated. Even a large pneumothorax cannot alter the dependence of pulmonary motion upon thoracic motion up to the point where the intrapulmonary pressure is atmospheric or positive during the entire respiratory cycle. At this point ventilation must cease. According to Boyle's law, the expiratory increase of intrapleural pressure reduces a 1000 c.c. pneumothorax (at inspiration) only about 10 c.c. under the assumption that intrapleural respiratory amplitude between inspiration and expiration is equal to 10 cm. water, in other words, the compressibility of air introduces a practically insignificant lag between thoracic and pulmonary movement. Air introduced into the pleural cavity always causes two effects: (1) it reduces the volume of the lung, and (2) it expands the thoracic cage. The degree of the latter effect depends chiefly on the elastic properties of the chest wall and the mediastinum. Furthermore, when the total volume of the lung is decreased the residual air shows a greater percentage decrease than

does the vital capacity. If, as is usually the case, the collapsed lung contains lesions, the volume reduction of the diseased areas does not reduce the vital capacity. These three factors—expansion of the thoracic cage, reduction of residual air, and collapse of nonfunctioning parenchyma, combine to cause a reduction of the vital capacity after collapse which is considerably smaller than the amount of air inflated. For these reasons a collapsed lung *can* continue to be ventilated by the preoperative amount of air, and, even more, and by virtue of the close gearing of pulmonary and thoracic motions, the pneumothorax lung *must* continue to be ventilated, as long as the thorax moves and as long as the intrapulmonary pressure is not positive throughout the respiratory cycle.

These theoretical deductions are amply confirmed by spirographic measurements on patients and on experimental animals, by direct observations of collapsed lungs and by roentgenological studies.

Figures 1, 2 and 8 present roentgenological evidence of the respiratory motion of collapsed lungs.

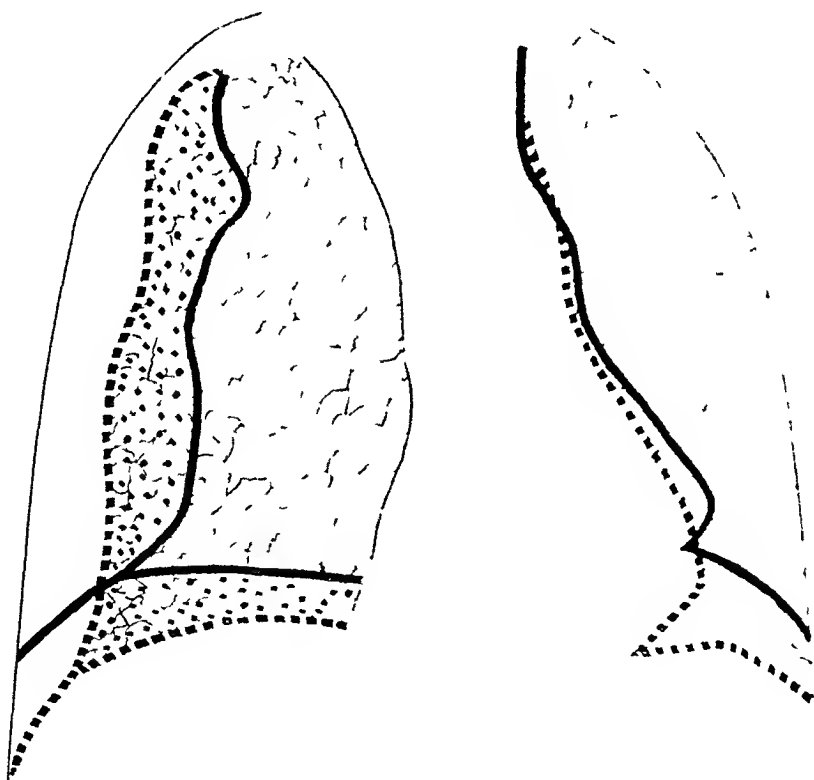


FIG 1 Superimposed tracings of a pneumothorax lung in deepest inspiration and in deepest expiration to show the respiratory movement of the collapsed lung. The heavily dotted area shows the increase in size of the lung at inspiration over its size at expiration.
 — tracing at expiration
 --- tracing at inspiration

Some limiting conditions must be mentioned. In the presence of an easily shifting mediastinum, the respiratory pressure changes cause a shifting of the mediastinum and a shifting of the lung *en bloc*, thus reducing the ventilation of the lung, as shown in figure 3.

When the diaphragm is paralyzed on the pneumothorax side, its paradoxical movement, activated by the intrapleural pressure changes, reduces the pulmonary ventilation. Paradoxical diaphragmatic movement occurs also in positive-pressure pneumothoraces without diaphragmatic paralysis. In positive pressure pneumothorax, if and when thoracic motion continues, the respiratory pressure changes cause only mediastinal shifting and paradoxical diaphragmatic motion, but no pulmonary ventilation.



FIG 2 Right lung, collapsed by pneumothorax. (a) in deepest inspiration, (b) in deepest expiration, to show the respiratory movement of the collapsed lung.

In order to find out how much a pneumothorax lung is ventilated, it is necessary to know the extent of mediastinal shifting, the degree of diaphragmatic paradoxical movement, and—last but not least—the amplitude of the thoracic (and diaphragmatic) movements. In uncomplicated pneumothoraces, the thoracic movements decrease but slightly. In the presence of pleural effusions and increasing fibrosis of the parietal pleura, thoracic movements are markedly reduced.

After proper consideration of all these factors it can be concluded that in subatmospheric pneumothoraces the collapsed lung continues to move. The incontrovertible proof of this statement is given by bilateral pneumothorax in which two collapsed lungs maintain normal gaseous exchange.

Regions of diseased pulmonary parenchyma, such as infiltrations, fibrosis,

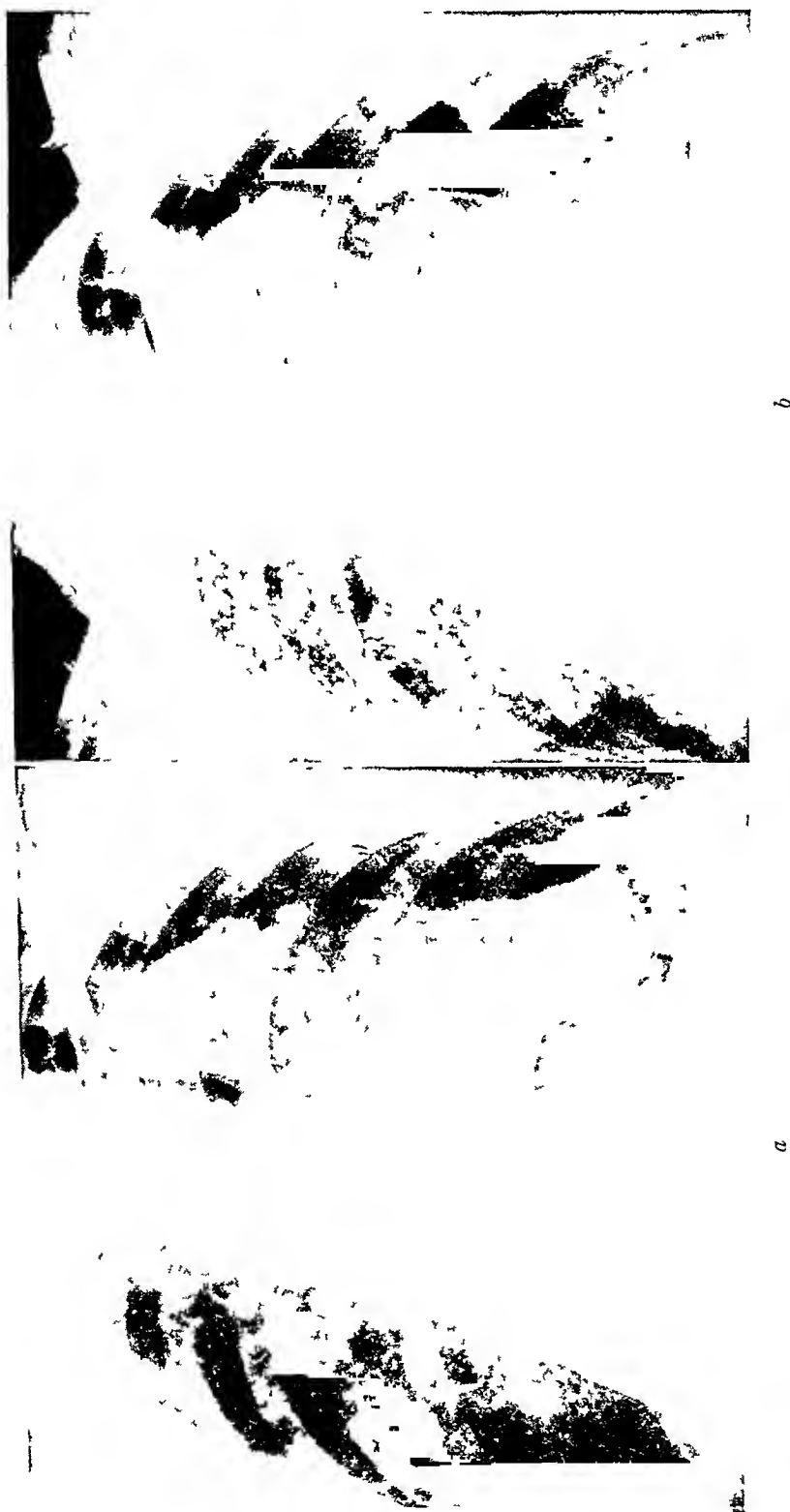


FIG. 3. Pneumothorax in the presence of a shifting mediastinum. (a) in deepest inspiration, (b) in deepest expiration. There is a marked shift of the mediastinal structures and of the right lung toward the left side during expiration. Mark that only the expiration film demonstrates the herniation of the mediastinum.

more or less fibrotic cavities, increase the normal elastic tension of the pulmonary tissue. When the pulmonary tissue relaxes, due to the reduction of the total volume of the lung, the parts under increased elastic tension will obviously retract more than the normal tissue. This is the basis of so-called selective collapse which is operative both in pneumothorax and, to a more limited degree, in diaphragmatic paralysis. In pneumothorax its manifestation is frequently prevented by adhesions inserted directly over the lesions. When selective collapse occurs, selective rest may occur as well. The less extensible, and hence more retracted, diseased portions are less easily expanded by the respiratory pressure changes, and in the ideal case they may be at complete rest while the uninvolved tissue functions fully. This ideal case depends upon a delicate balance between the differential elastic tensions of normal and diseased tissue on the one side, and on the level and the amplitudes of the intrapleural pressure on the other side.

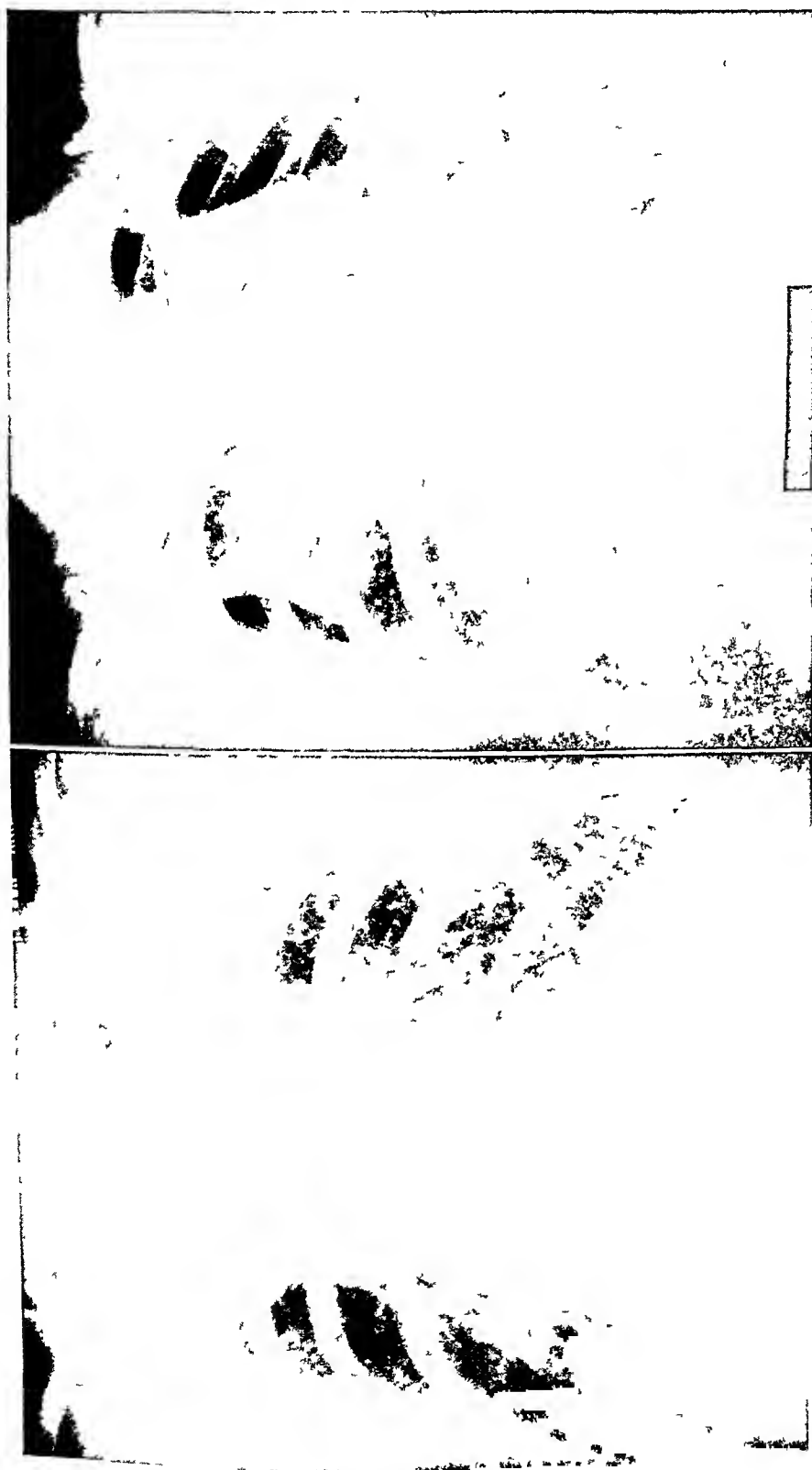
As far as other therapeutic collapse measures are concerned, similar considerations must be applied. In phrenicectomy, the piston action of the diaphragm is abolished, but costal motion continues, and is usually increased as a compensating mechanism. Hence, no functional rest can be expected from diaphragmatic paralysis. In an extensive thoracoplasty plus phrenicectomy, and in intercostal neurectomy, thoracic motion may become totally abolished, and then pulmonary rest is achieved, but this can be expected only in extensive and complete operations.

Summarizing the question of rest, it may be concluded that collapse may or may not establish mechanical rest for diseased parenchyma, that rest is frequently not procured in unquestionably successful procedures, and that therefore rest cannot be the sole, nor the dominant factor enhancing healing under collapse therapy.

(2) *Elastic Relaxation* Pulmonary collapse, i.e., reduction of total pulmonary volume, always causes elastic relaxation, regardless of the method by which collapse is induced. Relaxation diminishes or eliminates elastic tension which counteracts the natural shrinking tendency of scar tissue, it abolishes the traumatizing effect of the continuous strain on tissue under high elastic tension, and it allows cavity walls to approximate, thus establishing the mechanical prerequisite for spontaneous healing processes. The maximum elastic recoil occurs, unless prevented by adhesions, where the tissue is under highest elastic tension, that is, in the diseased portions of the lung. The pneumothorax lung assumes (in the absence of adhesions) the shape determined by its own differential elastic tensions, while the normally expanded lung is strictly dependent on the configuration of the thoracic cage. Pneumothorax liberates the lung as far as shape is concerned, but as far as motion is concerned it remains dependent on the thoracic cage within the limitation mentioned above.

The selective retraction of diseased portions of the lung in pneumothorax is clearly shown in figures 4 and 5.

* "Complete" is used here in a practical clinical sense. Strictly physically speaking absolute rest would be possible only if the diseased tissue were completely non-distensible.



b

a

FIG. 4 (a) before pneumothorax, (b) eight months later, following bilateral pneumothorax. The upper portion of the right lung is selectively collapsed, the lower portion of the right lung is almost completely expanded. In the left upper region, selective collapse is prevented by adhesions.

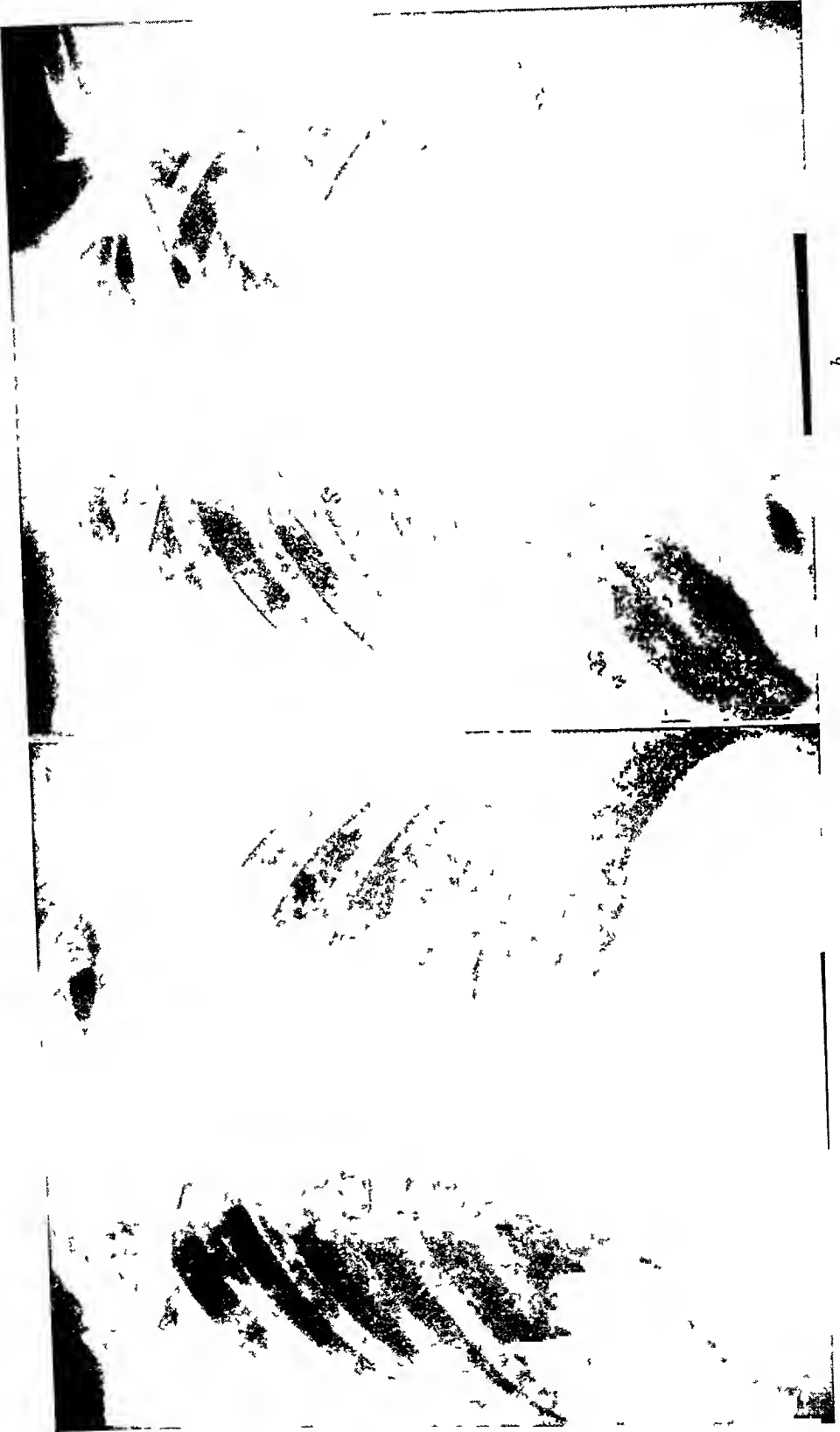


FIG 5 (a) before pneumothorax, (b) five and a half months later, following bilateral pneumothorax. Well defined selective collapse of both upper lobes

Elastic relaxation produces conditions obviously favorable for healing and it is a constant factor in all forms of collapse therapy. It seems justified, therefore, to regard elastic relaxation as an important, and probably the most important factor in enhancing healing under collapse therapy. It is therefore of greatest importance to assure it. In a pneumothorax adhesions inserted over parenchymal lesions may completely prevent elastic relaxation, and exert an elastic strain whose inspiratory and expiratory variations may be greater than before collapse. The usual roentgenographs, taken at maximum inspiration, furnish often misleading and always made-



FIG 6 (a) deepest inspiration, (b) deepest expiration. These two roentgenograms show the marked difference in the *apparent* size of the pneumothorax cavity. The inspiration picture might wrongly suggest that the lower lobe is adherent to the chest wall.

quate information of the collapsed lung, because (1) they show the intrapleural conditions in an unphysiological respiratory phase which the patient never assumes under natural conditions, and (2) they represent a static picture of the lung while interest should properly be centered on its dynamics.

Roentgenographs taken in maximum inspiration and in maximum expiration add significant information. While neither maximum inspiration, nor maximum expiration is a physiological phase the normal respiratory cycle lies somewhere near the middle of these two extremes, and the direc-

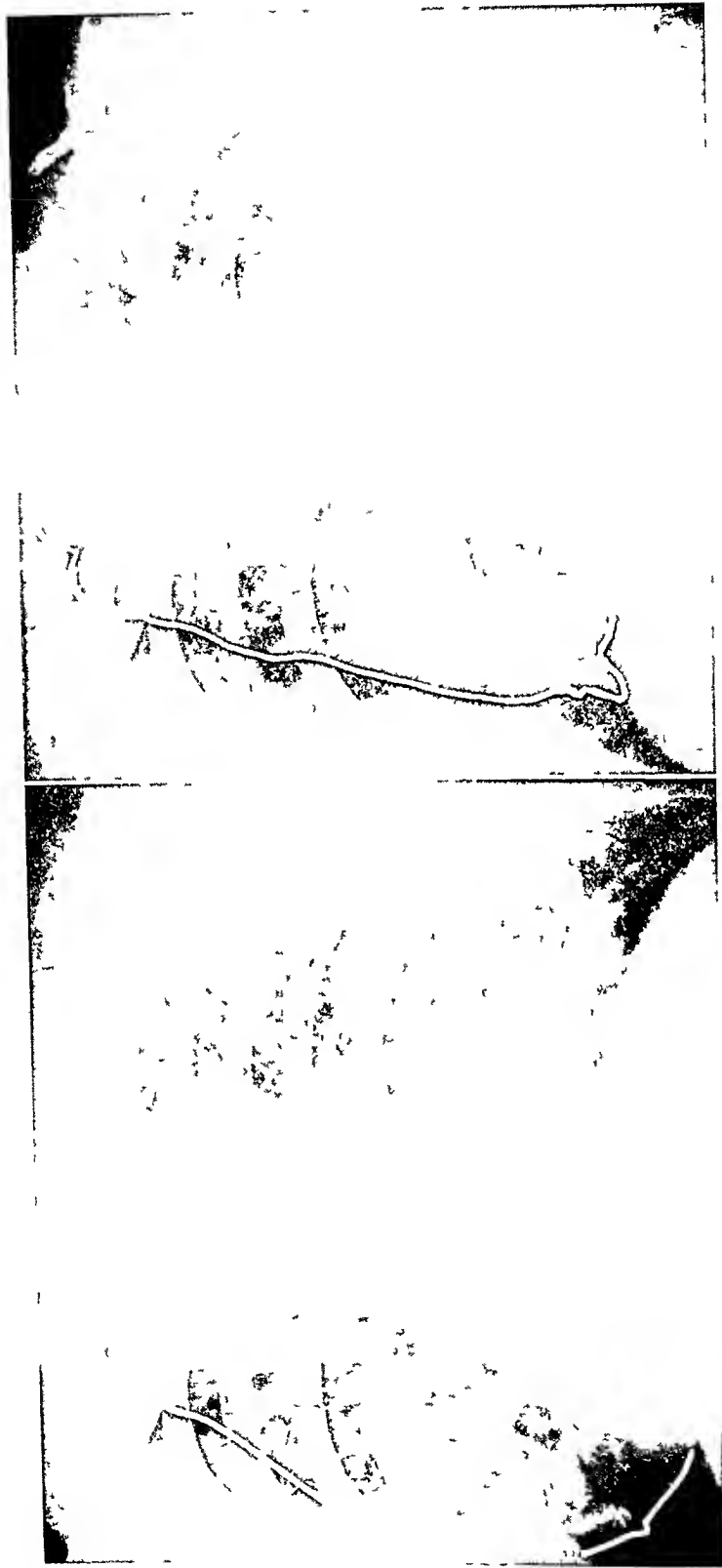


FIG 7 (a) deepest inspiration, (b) deepest expiration. The inspiration picture shows a slight collapse of the left lung with the lower lobe touching the chest wall and the mediastinal structures in normal position. The expiration film shows a moderate collapse of the entire left lung, the mediastinal structures markedly deviated to the right and a marked collapse of the right lung, particularly in its lower portion.

tion of forces operative in the chest is correctly shown. Inspiration and expiration films indicate roughly the actual degree of collapse (figure 6), the approximate degree of mediastinal shifting, the possible paradoxical movement of the diaphragm, the amount of contralateral collapse (figures 3 and 7), and—most important of all—they may demonstrate the presence of elastic strain produced by adhesions (figure 8). In addition to this, the expiration film shows, after small initial inflations, much more clearly the presence of a pneumothorax (figure 9). The comparison of the two films makes possible an approximate estimation of the degree of antero-



FIG 8 (a) deepest inspiration, (b) deepest expiration. The expiration film shows clearly the marked pull which the adhesion in the third anterior interspace exerts on the lung. The respiratory movement of the collapsed lung is clearly shown, not only by its increase in volume but by its greater transparency in inspiration.

posterior collapse. Inspiration-expiration films, properly interpreted, yield incomparably more information than a set of stereo-films taken at inspiration.

(3) *Hyperemia, Blood Stasis, Relative Anemia*. The changes that collapse causes in the blood circulation of the lung are the subject of numerous discussions and of extensive experimental and pathological studies. Without entering here into a lengthy discussion of the subject it should be emphasized that this problem is exceedingly complex and the technical and methodological difficulties of its experimental approach are well realized.

The Fick principle of estimating the blood flow is limited in its application because, by this method, only the fully aerated portion of the blood is measured, thus making it impossible to ascertain that amount that may flow through nonventilated portions of the lung. However, it is important to remember that it seems fairly well established that in uncomplicated pulmonary collapse the arterial blood is, as a rule, normally oxygenated. Since, as was pointed out, collapsed lungs may be ventilated by a normal, a larger, or a smaller than normal, amount of air, it appears very suggestive—and consistent with observational data—to think that a parallelism exists between



FIG 9 (a) deepest inspiration, (b) deepest expiration. These roentgenograms show how much more easily a small pneumothorax is visualized in expiration than in inspiration.

ventilation and circulation. This is confirmed by direct experimental observations on normal animals which indicate that the pulmonary blood flow increases during inspiration and decreases during expiration. If the above assumption is correct it is obviously impossible to make a categorical statement about hyperemia or anemia in a collapsed lung since either condition may prevail, depending on the state of ventilation. In collapsed lungs of long standing—the only ones that are of therapeutic interest—ventilation is probably decreased as a rule, hence relative anemia should be expected, and this seems to be the usual postmortem finding. Whether such anemia, when

it exists, has a definite therapeutic effect is undecided, it has been suggested that it may stimulate fibrosis

(4) *Anoxemia, Increase in Carbon Dioxide* These two factors are claimed to be of great therapeutic significance by producing a gaseous milieu unsuitable for the life of the tubercle bacillus. It is well established, however, that the tubercle bacillus, although a strict aerobic organism, continues to grow "until the last atom of oxygen is consumed," and is not inhibited by atmospheres containing 10 to 50 per cent of carbon dioxide. Obviously it is impossible that bactericidal degrees of anoxemia or of carbon dioxide concentrations exist in a collapsed lung. Even lesser degrees would be inconsistent with normal oxygenation of arterial blood in collapse therapy. While it is possible that minor degrees of anoxemia and of carbon dioxide increase may be less favorable for the activity of the tubercle bacillus than the normal gaseous tension in the lung, these changes—if and when they exist—can play only a minor therapeutic role.

(5) *Stasis of Lymph* Experimental evidence is convincing, though not entirely undisputed, that the lymph flow is slower in a collapsed than in a normally expanded lung. This fact may largely explain the beneficial influence that collapse so often exerts on toxic symptoms. By virtue of the slower lymph flow, toxic products are considerably more diluted in the blood stream than before collapse. It is probable, too, that lymph stasis exerts a stimulating effect on fibrosis, morphological observations show that fibrosis develops in diseased and collapsed lungs particularly in the perilymphatic tissue.

(6) *Atelectasis, Bronchial Obstruction* Atelectasis according to strict medical usage, though not according to etymology, means complete airlessness of pulmonary tissue. Incomplete atelectasis is therefore a *contradictio in adjecto* and this term should not be used. Uncomplicated collapse with subatmospheric pressure never leads to atelectasis. Atelectasis cannot be produced by external pressure on the lung but only by bronchial obstruction with subsequent absorption of the alveolar air, or by its functional analogue—a non-ventilated lung (positive pressure pneumothorax, otherwise completely immobilized lung). Bronchial obstruction, according to postmortem observation, is extremely rare in lungs collapsed on account of tuberculosis. Bronchial stenosis or obstruction, particularly if a bronchus draining a cavity is affected, is, as a rule, a grave complication with all the alarming symptomatology and the potentially perilous developments due to retention of secretion. It is therefore most unlikely that bronchial obstruction is—as has recently been claimed—the major healing mechanism of cavities and other tuberculous lesions in the lung. Pathological evidence for the therapeutic effect of bronchial obstruction is lacking. Furthermore, it would appear that the clinical and roentgenological diagnosis of atelectasis which appears so frequently in the recent literature, is usually poorly substantiated. Due to the mechanism of collateral respiration the obstruction of a small

bronchus does not lead to atelectasis so that the diagnosis of so-called lobular atelectasis rests on most uncertain ground. It is fully consistent with this view that foci healed by fibrosis in a collapsed lung are regularly surrounded by non-atelectatic, and frequently by emphysematous parenchyma.

When atelectasis does occur it does not *per se* cause fibrosis as is often assumed. So-called collapse-induration is not the result of simple atelectasis, but of atelectasis plus inflammation. If uncomplicated atelectasis would cause fibrosis one would expect to find, following complete thoracoplasties, that the whole lung would be fibrosed. The usual finding is, however, that the tuberculous lesions are fibrosed, and that the intervening parenchyma is not.

(7) *Cessation of Spread in Collapsed Lung* Evidence of hematogenous spread in collapsed lungs, even in cases of generalized miliary tuberculosis, is very rare. The same thing is true of lymphatic and, to a lesser degree, of bronchogenic spread. These phenomena are not well understood. The reduction of the lymph and blood stream in a collapsed lung must be important factors. The tortuous course of bronchi in a collapsed lung and under certain conditions, the diminished momentum of the air stream, may cause the diminution of bronchogenic propagation.

In many particulars, knowledge of the physiological effect of pulmonary collapse is incomplete and understanding is unsatisfactory. To mention one practical and outstanding example there is no convincing explanation of the fact that collapse seems to enhance resorption of exudative infiltrations. It is hoped that the recently revived pneumothorax treatment of lobar pneumonia may furnish observations not only to confirm, but also to explain this fact.

SUMMARY

In the healing of tuberculous lesions under collapse therapy, the following factors—roughly in order of their importance—seem to be operative:

- 1 Elastic relaxation diminishes or eliminates elastic strain on diseased tissue, thus enhancing scar contraction and closure of cavities.

- 2 Relative, and in some cases absolute rest of foci of disease is produced by the mechanism of selective collapse, by splinting or immobilizing the thoracic cage, or by procedures enforcing localized relaxation and immobilization.

- 3 Actual compression (positive pressure pneumothorax) helps to collapse stiff-walled cavities and to stretch adhesions.

- 4 Tortuosity of bronchi and the slowing of the air stream in a collapsed lung help to diminish bronchogenic spread.

- 5 The slowing of the blood and lymph stream prevents hematogenous and lymphatic propagation. Diminution of the lymph stream may reduce toxemia.

6 It is possible, but not proved, that relative anemia and lymph stasis may stimulate fibrosis

7 A reduction of the oxygen tension and increase in the carbon dioxide tension in the pulmonary tissue may possibly produce conditions that are somewhat less favorable for the life of the tubercle bacillus

I wish to express my thanks to Dr C A Thomas and Dr S C Davis for their permission to use in this paper clinical and roentgenological material from the Southern Pacific Hospital in Tucson

LYMPHEDEMA OF THE EXTREMITIES ETIOLOGY, CLASSIFICATION AND TREATMENT, REPORT OF 300 CASES

By EDGAR V ALLEN, M D , F A C P , and RALPH K GHORMLEY, M D ,

Rochester, Minnesota

GENERAL information about lymphedema tends to be somewhat confused and vague. This situation is largely the result of the relative rarity of the condition, of an inadequate knowledge of its etiology, bacteriology, and pathology, and of the lack of a comprehensive classification. Although it is impossible to rectify all these shortcomings, we feel that a presentation of the pertinent data from the records of 300 cases observed at The Mayo Clinic in the previous 10 years offers an opportunity to fill some of the gaps in knowledge. To this end, we are describing the condition, offering a clinical classification, and presenting what is known regarding etiology, diagnosis, and treatment. Aids to such a presentation are furnished by recent excellent work on the anatomy and physiology of lymph and lymph vessels, well illustrated by the work of Drinker and Field. These facts regarding the anatomy and physiology of lymph vessels and lymph are so important for an understanding of lymphedema that it seems advisable to review them briefly.

DEFINITION OF TERMS

Lymph is a fluid obtained from lymph vessels. Tissue fluid is found in the region outside of the blood and lymph capillaries in the cellular interspace. Plasma is the unclotted fluid of the blood. Lymphedema is a swelling of soft tissues which is the result of an increased quantity of lymph. Elephantiasis has been defined as a "progressive histopathologic state characterized by a chronic inflammatory fibromatosis or hypertrophy of the hypodermal and dermal connective tissue,"²¹ but the term has been used loosely to apply to a variety of conditions which produce enlargement of the extremities. We suggest, therefore, discontinuation of use of this term, which adds confusion to medical terminology.

ANATOMY

Lymph vessels either are modified veins or arise in situ from mesenchymal cells. They are closed vessels which possess an unbroken endothelial lining, bathed on the outside by tissue fluid. In general, there is more lymphatic than hematic capillary surface. Every main blood vessel has an accompanying lymph vessel.²⁵ The lymph vessels are as richly supplied

* Read at the Philadelphia meeting of the American College of Physicians, May 2, 1935.

From The Mayo Clinic, Rochester, Minnesota

with valves as are the veins⁵ India ink injected between two ligatures into the lumen of an artery appears in the lymph vessels around the artery by passing through intracellular stomas and directly through the cells of the arterial wall¹⁷

There are a superficial and a deep system of lymph vessels in the leg but there is no communication between them except through the popliteal and inguinal lymph nodes³⁰ In animals most of the superficial lymph vessels of the leg and foot, as well as some of the deep lymph vessels that drain the muscles of the leg, terminate in the popliteal lymph node From this node large efferent trunks course along the femoral vessels to end in the external iliac nodes, just distal to the bifurcation of the aorta Many of the superficial lymph vessels of the thigh and upper part of the leg drain into the inguinal lymph nodes, which in turn have efferent vessels terminating in the external iliac nodes The deeper lymph vessels in the muscle sheaths of the thigh eventually enter trunks that accompany the main femoral lymph vessels and drain into the large iliac nodes²⁷ All the lymph vessels of the leg both superficial and deep, join at the groin and pass along the external and common iliac vessels through the iliac nodes The lymphatic trunks at the root of the leg hug the veins closely, and may even be embedded in the adventitia of their walls They are enclosed in a tough fibrous sheath along with the great blood vessels¹²

The superficial lymph vessels of the third, fourth and fifth fingers pass to the dorsum of the digits, then upward and around the ulnar side of the forearm to the flexor side of the forearm, where they join those coming from the entire ulnar side of the forearm and pass upward into the axillary nodes, with or without intervention of the cubital lymph node Those of the index finger and thumb pass upward on the dorsum of these digits, then around the radial side of the forearm to the flexor surface, where they join those coming from the radial side of the forearm, and pass upward to the axillary nodes An occasional lymph vessel may pass upward on the extensor surface of the forearm to well above the elbow, where it turns sharply around the ulnar side of the arm to its inner side and thence to the axillary nodes The superficial lymph vessels of the arm empty into the axillary nodes or, much less frequently, into the deltoideopectoral or supraclavicular nodes The deep lymph vessels of the arm run with the large vessels to empty into the axillary lymph nodes, with or without the intervention of the deep cubital lymph nodes The superficial and deep lymph vessels are connected at the elbow by the deep and superficial cubital lymph nodes³

Regeneration and Collateral Circulation If a large lymph vessel is cut, the circulation is carried on by collateral vessels Later, the passage between the two cut ends regenerates, and the collateral circulation recedes Collateral lymph vessels develop a few days after ligation of the main trunks⁶ Regeneration of lymph vessels is rapid They cross the scar of

an incision as early as the fourth day, and by the eighth day regeneration is physiologically adequate²⁶

PHYSIOLOGY

The endothelium of the lymph vessels is more permeable than that of blood capillaries. It does not possess any selective absorptive power, but merely admits material that is forced on its outer surface. Particles of microscopic dimensions which are deposited in various parts of the body, cannot move far except by entering and passing along the lymph vessels.

Pressure and Circulation of Peripheral Lymph Active or passive contraction of skeletal muscles plays the most important part in the movement of lymph of man, the valves of the lymph vessels serve as the most important accessory arrangement for moving lymph forward.⁵

The circulation of lymph is rapid, but it varies greatly. Trypan blue that is injected into the lymph vessel of the foot of a dog may reach the receptaculum chyli in 10 seconds, and sodium salicylate that is injected similarly can be detected in the lymph of the thoracic duct in one minute and 20 seconds. Bromphenol blue, when injected intravenously, appears in the cervical lymph in two and a half minutes.

The pressure of lymph varies considerably, depending on the animal studied and the situation at which the pressure is determined. Ordinarily it is only equivalent to a few millimeters of water. It is greatly increased by exercise and inflammation.

Coagulation of Lymph Lymph contains fibrinogen and prothrombin, but it clots more slowly (from 10 to 20 minutes) than blood (from four to six minutes), owing to deficiency of thromboplastic substance ordinarily supplied in a large degree by blood platelets that are absent in lymph. This deficiency is corrected and coagulation of lymph occurs whenever cells in contact with the lymph stream undergo necrosis, or whenever lymph stasis and living bacteria in lymph coexist.²⁴ When thrombosis of the lymph vessels occurs, the thrombi contract and shrink away from the wall of the vessel, leaving adequate space for the circulation of lymph, except when the coagulating process is progressive. Lymph vessels may be completely filled with thrombi in the region of a phlegmon.

Various foreign substances injected into an area of severe inflammation do not pass into the lymphatic capillaries, but the same substances, when injected intravenously, accumulate rapidly in the inflamed area. Both observations are explained on the basis of thrombosis of the lymph vessels and the presence of a fine network of fibrin which obstructs the flow of lymph away from the inflamed area.*

EXPERIMENTAL STUDIES OF LYMPHEDEMA

Complete excision of the iliac and inguinal lymph nodes of animals does not produce lymphedema which, however, can be produced temporarily by

* Unless a specific reference has been given in the preceding paragraphs, the authority is the monograph of Drinker and Field.⁴

dividing the limb of a dog transversely, leaving only the carefully denuded femoral artery and vein, and by suturing the edges of the wound ²⁶

The rôle that lymphatic occlusion plays in phlegmasia alba dolens, which ordinarily has been considered to be the result of venous thrombosis, has



FIG 1 Lymphedema precox affecting a woman aged 18 years. At the age of 13 years there was sudden swelling of the right leg and two years later the left leg became swollen.

been studied experimentally by Homans, Homans and Zollinger, and Zimmermann and de Takats. Homans believed that experimental and clinical phlegmasia alba dolens was caused, in a large degree, by lymphatic obstruction, but Zimmermann and de Takats could not find support for this view, with their experiments.

The problem of the production of chronic lymphedema of animals had not been solved until recently when Homans, Drinker, and Field reported the reproduction of characteristic lymphedema in dogs by injecting a solution of quinine and a suspension of silica into lymph vessels in several areas, which produced a thrombosis of these vessels. A steadily increasing content of protein was noted in the lymph, the deep layers of the skin and subcutaneous tissues steadily became the sites of an increasing fibrosis which was evidence of active proliferation of connective tissue. Attacks of acute lymphangitis, which produced fever and prostration, occurred spontaneously. Hemolytic streptococci could be recovered from the edematous tissue at the beginning of the attacks but never at any other time. When thorotrast was injected into the edematous legs, the direction in which it flowed depended entirely on gravity, it ran toward the foot just as well as away from it, through capacious valveless series of pond-like and river-like lymph vessels.

ETIOLOGY OF LYMPHEDEMA OF MAN

Lymphedema, which affects human beings, appears to have a multiple etiology. The mechanism of its production which is, however, apparently the same in all cases, is predicated on clinical and experimental observations. Lymph stasis occurs primarily as a result of obstruction that is produced by inflammatory or noninflammatory processes, or by lymphangiectasis, which occurs in association with congenital lymphedema. When obstruction occurs, the intralymphatic pressure increases, and causes dilatation of lymph vessels with subsequent insufficiency of the valves, forcing lymph to seek new channels which are supplied inadequately with valves. Since valves are very important in causing the lymph to move centrally, incompetence of the valves causes further stasis of lymph. The protein content of the lymph increases and fibroblasts proliferate rapidly since the lymph is an excellent culture medium for the growth of fibroblasts. This fibrosis contributes further to lymph stasis. As a result of the increased quantity of lymph in the tissues, attacks of acute inflammation may recur, producing thrombosis of lymph vessels, more stasis of lymph, and, hence, more fibrosis. The cycle, which is a vicious one, consists of stasis of lymph, fibrosis, inflammation with further stasis, and, hence, more fibrosis.

PATHOLOGY

Excellent studies of lymphedematous tissues are available. Unfortunately, specific findings have not been correlated with the particular type of the disease, or with the phase of the disease at the time the tissue was secured for study. Perhaps this correlation is not possible but this should be determined. While morphologic studies have determined the basis of enlargement of the limb in cases of lymphedema, they have shed but little light on etiology. It is to be hoped that the experimental production of lymphedema will lead to orderly presentation of the morphologic changes

which occur as minimal lymphedema progresses to marked lymphedema and hypertrophy of the limb. Our studies, which are incomplete, indicate that the morphologic changes, which are present in cases of congenital lymphedema, are characteristic of this condition.²⁰ The subcutaneous tissue is increased in thickness and the adipose tissue is replaced by enlarged lymph spaces and by connective tissue. Thrombosis of lymph vessels and of blood



FIG 2 Lymphedema precox with secondary cellulitis affecting a woman aged 23 years. The right leg had swelled at the age of 10 years. When the patient was 20 years old, acute cellulitis and lymphangitis had involved both legs following which both legs had remained swollen.

vessels, and evidence of inflammation are routinely absent. Pathologic changes reported in various types of lymphedema are variable. Thickening of the skin and subcutis, replacement of adipose tissue by enlarged lymph spaces and by connective tissue, atrophy of muscle, nerve fibers, and sweat glands, infiltration of most cells, especially lymphocytes and leukocytes, and a variety of other changes, have been described.^{7, 28, 31}

CLASSIFICATION OF LYMPHEDEMA OF THE EXTREMITIES OF MAN ¹

The cases of lymphedema studied lend themselves to division into two main groups, inflammatory and noninflammatory, the terms infectious and noninfectious could be used as well. The division into the two groups indicates the original state, lymphedema which is originally noninflammatory may be complicated eventually by inflammatory changes. Most cases of lymphedema may be classified without difficulty according to the tabulation. The classification is purely clinical.

NONINFLAMMATORY LYMPHEDEMA

Primary Lymphedema "Lymphedema precox" is an original term applied to a definite clinical syndrome manifested in 93 cases in the group studied. It affected female patients predominantly (87 per cent of the cases), and in the majority of instances (65 per cent) had its onset between the ages of 10 and 24 years, inclusively. The term "precox" is used here

CLASSIFICATION OF 300 CASES OF LYMPHEDEMA

A Noninflammatory		
I Primary		Cases
Precox		93
Congenital		
1 Simple		12
2 Familial (Milroy's disease)		0
II Secondary		
Malignant occlusion		32
Surgical removal of lymph nodes		61
Pressure		1
Roentgen and radium therapy		3
B Inflammatory		
I Primary (single or recurrent acute and chronic)		41
II Secondary (single or recurrent acute and chronic)		
Venous stasis		13
Trichophytosis		5
Systemic diseases		5
Local tissue injury or inflammation		33
Filariasis		1

to denote an early development, in many of the cases in this group the onset of symptoms occurred at puberty, and the incidence of onset in adolescence was impressive.

The swelling occurs spontaneously and without known cause, at the onset, the patient ordinarily notices a puffiness about the foot or ankle. The edema is worse during long periods of activity, during the menses and in warm weather. Rest in bed and elevation of the extremity produce temporary disappearance of the edema that may affect one lower extremity exclusively (70 per cent in this series) or both legs simultaneously, or one extremity may swell months or years after the opposite member has become involved.

The edema ordinarily progresses up the leg slowly, and eventually the entire limb becomes edematous over a period of months or years. The

spread of the edema may, however, be much more rapid, the entire limb may be involved within a few days or weeks. In many instances, swelling is limited to the foot and ankle or does not extend above the knee. Frequently, this particular state is doubtless merely a phase of a progressive condition, but in other instances it seems to represent the maximal degree of extension of the edema.

Gradually the swelling, whatever its limitations, becomes more marked, elevation and rest in bed cause its reduction but not its disappearance. The smooth skin becomes roughened, and the hitherto soft edema becomes resistant to pressure. In addition to enlargement of the limb due to edema, there is actual hypertrophy of tissue, and the limb becomes unsightly, ungainly and uncomfortable. A dull, heavy sensation is present, but there is no actual pain.

The entire course of the swelling is ordinarily one of smooth progression, acute lymphangitis and cellulitis occur infrequently (in 13 per cent of the cases studied). Ulceration of the skin does not occur. The entire history is ordinarily that of conversion of a normal limb into a swollen one, nothing else is noteworthy.

The cause of lymphedema precox is obscure. The predominant incidence among female patients, the onset in the majority of cases during adolescence and the accentuation during menstruation tend to indicate that the reproductive organs play a part in the condition. Possibly the additional load thrown on the lymph vessels by rapidly developing reproductive structures induces a functional incompetence of the lymph vessels or allows entrance of infection into the lymph trunks and nodes in the pelvis. Even minor degrees of functional inadequacy, through obstruction in the pelvis, might lead to dilatation of the lymph vessels below, with incompetence of the valves, particularly among women, whose subcutaneous tissues offer little support. The resulting interference with the free passage of tissue fluid into the lymph vessels provides adequate encouragement for the growth of fibroblasts and further obstruction by connective tissue. Homans, Drinker, and Field reported a case in which the lymphedema apparently was of the precox type. At exploration, greatly enlarged lymph vessels were found in the pelvis, this was an indication of obstruction proximally.¹³ It is possible that the entire explanation rests on a congenital underdevelopment of lymph vessels, or their inability to develop quickly enough to supply adequately tissues that are growing rapidly. Limitation of the disease to the lower extremities is striking, and it indicates that gravity is an important factor in the development.

Congenital Lymphedema This may be either simple or familial. In both types, lymphedematous swelling, usually of one lower extremity, is present at birth. There may be actual hypertrophy of the limb which is the result of fibrous hypertrophy. In other instances, the skin is soft, and the edema is less resistant to pressure. The two forms do not vary, except that in the simple type blood relatives are not similarly affected. In the

familial type, several persons in the same family have lymphedematous swellings of one or more extremities. The familial type, known as Milroy's disease, was first described by him as a clinical entity in 1892. Milroy said

"Briefly stated, chronic hereditary edema consists in a firm edema. It is limited in extent to the toes or a part or the whole of one or both feet, or



FIG 3 Congenital lymphedema of the right leg affecting a boy 16 years old

of one or both legs. It never extends above Poupart's ligament. It is not painful or tender and is without constitutional symptoms. It arises from no apparent cause. Hereditary transmission is conspicuous in its behaviour."¹⁶

Milroy's original report was based on a study of six generations of a family of 97 persons, of whom 22 had lymphedema, 21 of the 22 having

been born with the condition. Variations from the criteria of Milroy have been so great that the term "Milroy's disease" as used concurrently, is largely without significance. Meige found only eight cases in four generations, the onset at puberty was striking. Under the title Milroy's disease, Hope and French reported 13 instances of this disease among 42 persons in five generations¹⁵, in no instance was the condition congenital, the time of onset ranged from infancy to manhood, and attacks of recurrent cellulitis and lymphangitis occurred. Familial lipodystrophy is apparently confused with Milroy's disease. There were no instances of Milroy's disease in our series of cases. Occasionally, a patient said that he or she believed that a relative was similarly affected with swelling of the extremities, but the details were vague, and in no instance was it proved that the lymphedema was both congenital and familial.

That the criteria of Milroy have been departed from is to be deprecated. Familial lymphedema is not Milroy's disease, according to Milroy's definition, unless the condition is congenital. Many of the cases called "Milroy's disease" are doubtless examples of lymphedema precox with a familial predilection. The marked hereditary and congenital features, which were present in Milroy's cases, have not been equaled in cases that have been reported by others. The situation that was recorded by Milroy may be unique. This constitutes further reason for close adherence to the diagnostic criteria that have been given. Recent pathologic studies of tissues which have been removed from patients who had congenital lymphedema, show that widely dilated lymph spaces and connective tissue occupy the space ordinarily taken up by subcutaneous tissue²⁰. The original lesion is apparently lymphangiectasis, a congenital malformation or one which was acquired in intra-uterine life. Lymph stasis results and fibrosis occurs.

Secondary Lymphedema This may be the result of malignant occlusion of lymph vessels by metastasis of malignant disease of the breast, uterine cervix, uterus, vulva, prostate gland, bladder, testes, skin, or bones to adjacent lymph nodes. Such a possibility serves to emphasize the necessity of close scrutiny for evidence of malignant disease in all cases of lymphedema, since swelling may be the first outward manifestation. Pressure outside the lymphatic trunks perhaps occasionally, but rarely, produces lymphedema. The one case of lymphedema apparently due to pressure in this series seemed to follow the use of a truss for inguinal hernia. Secondary, noninflammatory lymphedema may occur in cases of Hodgkin's disease, or lymphosarcoma, or it may be associated with multiple hemorrhagic sarcoma, which has been described by Kaposi¹⁸, or it may follow surgical removal of lymph nodes and lymph vessels for malignant disease distally situated or for tuberculosis or metastasis of malignant disease. The last named condition is the elephantiasis chirurgica of Halsted. Such a condition is not uncommonly seen following radical amputation of the breast and the removal of the axillary lymph nodes for carcinoma. The lymphedema may occur with or without intercurrent attacks of lymph-

angitis and cellulitis. The irregular interval at which lymphedema occurs after radical amputation of the breast is remarkable. Usually, the arm begins to swell on resumption of activity, but weeks, months, or even years, may pass before the extremity becomes edematous. In one instance, the arm was free from swelling for nine and a half years, there was no evidence of the recurrence of malignancy to account for the edema, and cellulitis



FIG 4 Congenital lymphedema of the right arm and right side of the face, affecting a girl four years old

and lymphangitis had not occurred. In such instances, it is possible that fibrosis may be induced by repeated irradiation, thus producing lymphatic obstruction, or that occult lymphedema, which has been present for years, has resulted in overgrowth of connective tissue and obvious edema. Unfortunately, there are no experimental data to explain the occurrence of edema after radical removal of the breast, experiments on animals reveal that extensive removal of lymph nodes does not cause edema. Why, then,

does this condition occur in man after extensive removal of lymph nodes? Halsted believed it was caused by infection following operation, either obvious or so slight as to avoid detection, or by recurrent attacks of cellulitis and lymphangitis. The question cannot be answered here. The answer may be inherent in the comparatively small number of experiments performed for the removal of lymph nodes of animals, lymphedema has not been demonstrated with these experiments, but neither does it occur in many instances following radical removal of the breast of a human being. If larger numbers of animals were observed over greater periods of time following surgical removal of lymph nodes, it is probable that lymphedema would be noted. The conclusion based on clinical observation cannot be avoided, surgical removal of, or metastasis to, lymph nodes may produce lymphedema.

Lymphedema may occur after treatment with radium and roentgen-rays. Whether such a result is brought about by the fibrosis caused by irradiation, or by metastasis of the malignant disease for which radiation is given, cannot be determined with certainty. Barker described a case in which radium irradiation for a disease, apparently incorrectly diagnosed as carcinoma of the uterine cervix, was followed by lymphedema.

INFLAMMATORY LYMPHEDEMA

General characteristics. The advanced stage of inflammatory lymphedema has been called "*elephantiasis nostras streptogenes*." All examples of inflammatory lymphedema, exclusive of the chronic form, have one feature in common, single or recurrent attacks of acute cellulitis and lymphangitis. The contrast between lymphedema of inflammatory origin and of the precox type is striking, in the former, progression is by a series of attacks which are impressive in the suddenness of onset, and striking in the severity of systemic reaction, in the latter, the history is one of slowly progressive edema. The usual victim of an attack of cellulitis and lymphangitis of an advanced grade is suddenly seized with a severe chill unpreceded by other symptoms, or, following a short period of distress in the extremity or in its proximal lymph nodes, his teeth chatter, the bed shakes and he becomes nauseated and vomits. His temperature is between 101 and 106° F., in a short time a small, reddened area spreads until a considerable portion of the extremity is swollen, red, hot and tender. The proximal lymph nodes are tender and swollen. The chills recur during a period of 30 minutes to an hour. The high fever persists for a period ranging from a few hours to two or three days, and is accompanied by marked malaise that may persist after the temperature returns to normal. The abnormal condition of the extremity recedes slowly over a period of from four to 14 days but, after all clinical signs of acute inflammation have disappeared, swelling is present in a greater degree than before the attack. The organism chiefly responsible for the attacks of acute inflammation is the streptococcus.²

Single attacks leave minor degrees of lymphedema, but successive attacks, which tend to occur progressively, more frequently produce increasing edema, each attack is a step toward the final stage, namely, marked lymphedema. The chronic form of lymphangitis of the spontaneous type is exceedingly rare. In such instances, the leg is persistently warmer than its companion member, and a reddish discoloration of the skin exists. In many instances, lymphedema following injury or infection develops without the intervention of acute attacks of lymphangitis and cellulitis or of clinical manifestations of chronic lymphangitis. The infection in such instances is considered to be subclinical. It should be emphasized that lymphangitis, whatever its nature, produces occlusion of lymph vessels by thrombosis which produces lymph stasis which in turn provokes further fibrosis and more stasis of lymph.

Primary Lymphedema This term signifies a condition resulting from single or recurring acute attacks or from chronic lymphangitis and cellulitis not secondary to any known local abnormality, such as venous or lymphatic stasis or extraneous infection. In many such instances, the lymphangitis appears to occur in much the same spontaneous manner as tonsillitis or phlebitis. In other instances, it may be due to infections introduced into the lymph vessels through minor portals of entry unnoticed by the patient. The acute attacks of lymphangitis and cellulitis have been described, each attack leaves a residue of increased edema. In the chronic form of lymphangitis, the edema is slowly progressive.

Secondary Lymphedema This term indicates a condition resulting from lymphangitis secondary to known causes. The lymphangitis may occur in single or recurrent attacks or in a chronic form. Chronic edema of venous origin may predispose to recurrent attacks of acute cellulitis and lymphangitis, and thus to progressive lymphedema, but such instances are uncommon, in light of the rather common occurrence of thrombophlebitis resulting in edema.

Trichophytosis about the toes may induce recurrent attacks of acute lymphangitis. The inflammation and the resultant edema are ordinarily limited to the foot and ankle. It is probable that an etiologic relationship exists in but a small percentage of instances in which trichophytosis and acute attacks of lymphangitis occur in the same patient. It is not clear whether the trichophytes themselves or secondary bacterial invaders are responsible, even when the trichophytic infection seems to be definitely related to the acute inflammatory attacks. Instances which strongly suggest that the Trichophyton is directly or indirectly responsible for the acute attacks are those in which marked evidence of trichophytic infections, such as desquamation and the occurrence of vesicles, precede the appearance of cellulitis and lymphangitis. Pregnancy and systemic diseases, such as influenza, typhoid fever, pneumonia, malaria, and filariasis, may lead to recurrent attacks of cellulitis and lymphangitis, and result in lymphedema. Except in cases of filariasis, it is possible that the original lesion is a thrombo-

phlebitis that produces lymphatic as well as venous occlusion, as shown by Homans,¹¹ and thus subsequent attacks of lymphangitis and, eventually, clinical lymphedema. Occasionally, conversion into the lymphedematous state proceeds without the intervention of attacks of acute inflammation, in such instances, it is assumed that a condition of chronic lymphangitis exists, or that the lymph vessels become obstructed by overgrowth of connective tissue which is, in turn, a reaction to stasis of tissue fluid. Tissue fluid acts as an excellent culture medium, fibroblasts grow and fibrosis

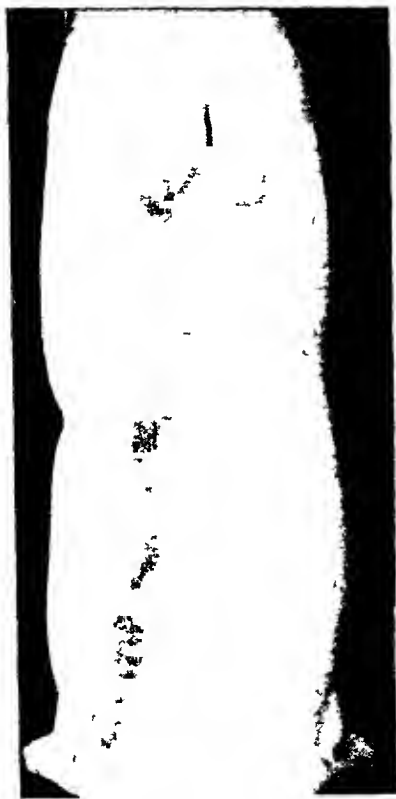


FIG 5 Secondary inflammatory lymphedema affecting a boy, aged 16 years. At the age of 13 years a "boil" appeared on the inner side of the left thigh, followed by swelling of the entire leg.

results unless the blood plasma is promptly returned to tubes lined with endothelium. It is worthy of note that filariasis was not demonstrated in any of the cases of lymphedema reported in this study. Clinical evidence of, or an antecedent history suggestive of, filariasis was present in but one case. A physician who had observed many cases of lymphedema caused by *Filaria*, in China, examined this patient and expressed the opinion that the condition was characteristically one of lymphedema caused by *Filaria*. An acute episode of inflammation did not occur while the patient was under our observation, and *Filaria* were not demonstrated in the blood, in many

instances, blood drawn from other patients at night was studied, but *Filaria* were never found. It is possible, if not probable, that filariasis existed in some of the cases reported, for it has been shown that failure to find *Filaria* does not exclude filariasis. The patients of The Mayo Clinic are drawn largely from northern climates where filariasis exists sporadically, if at all, and it is obvious that the absence of this condition as a cause of lymphedema would not hold in more southern locations where filariasis is common.

Local inflammation or injury of tissue most commonly leads to the production of lymphedema through the intermediation of single or recurrent attacks of lymphangitis or chronic lymphangitis. In the cases studied, such diverse causes as contusions, lacerations, surgical incisions, vesicles, abscesses, furuncles, burns, fractures, penetrating wounds, bites by dogs, tularemic abscesses, pelvic inflammatory diseases, and appendicitis were directly responsible. The acute attacks may occur weeks or months after the original trauma, which may not be associated with any marked clinical evidence of infection. Some stasis of lymph, subclinical in degree or unnoted by the patient, seems to exist, then, for some unknown reason, marked bacterial activity occurs, and an acute attack of cellulitis and lymphangitis is clinically apparent. It seems strange that minor abrasions should allow entrance of infection into the tissues, but Hudack and McMaster demonstrated that the slightest wound of the corium may tear lymph vessels open and permit material to enter them directly. In many instances, the lymphedema occurred following injury or infection without the intervention of acute attacks of inflammation, and seemed to be caused by chronic or subclinical inflammation and thrombosis of lymph vessels, or by minimal lymph stasis which provoked connective tissue overgrowth.

DIFFERENTIAL DIAGNOSIS

There is rarely any difficulty in distinguishing advanced lymphedema from other types of edema. The brawny indurated skin and the hypertrophied limb of advanced lymphedema bear little resemblance to manifestations of edema in other diseases. It is only when the lymphedema is not associated with changes in the appearance and feel of the skin that difficulty arises. Lymphedema can be distinguished without difficulty from the edema of general systemic diseases, such as myxedema, myocardial failure, nephrosis, nephritis or deficient proteinemia, when it is unilateral, when it is bilateral, a thorough examination is necessary to exclude these diseases. Sarcomas, lipomas, and neoplasms of the bone are almost uniformly unilateral, and they produce regional or localized swellings, whereas the edema of lymphatic obstruction is more uniform and extensive. When swelling of an extremity is localized, careful roentgenologic studies are invaluable from a diagnostic standpoint. Angioneurotic and cyclic edemas are characterized by intermittence, whereas lymphedema is more constant and disappears during the early phase only on elevation of the limb, well ad-

vanced lymphedema responds to this procedure incompletely. Enlargement of a limb in arteriovenous fistula is associated with dilatation of and increased pressure in the regional veins, analysis of the blood from these veins reveals an oxygen content approaching that of arterial blood. If the arteriovenous fistula is congenital, or was acquired before longitudinal growth of the bones ceased spontaneously, the limb is increased in length as well as in circumference. All these signs of arteriovenous fistula, except the increased circumference of the limb, are absent in lymphedema.

The edema of limbs occasionally noted in lymphosarcoma is probably of

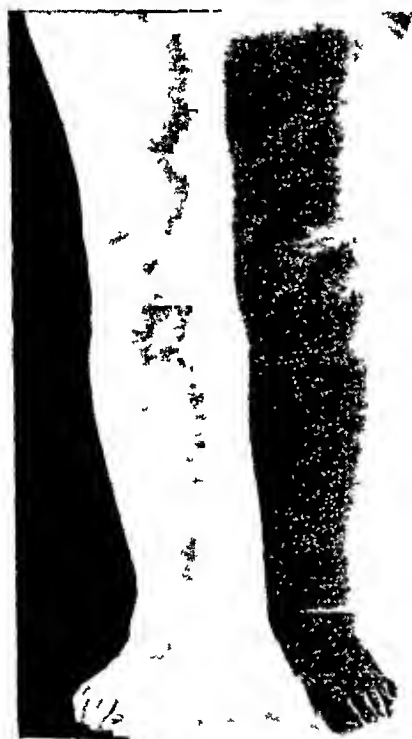


FIG 6 Secondary inflammatory lymphedema associated with trichophytosis, affecting a woman, aged 55 years. A vesicular, itching lesion of the skin of the toes, and of the dorsal and plantar surfaces of the left foot, had been present for four years. Attacks of acute lymphangitis and cellulitis recurred, and edema had been present for three and a half years. At the time of examination, trichophytes were found in the cutaneous lesions.

lymphatic origin, but recognition of the basic condition is important. Ordinarily, in cases of lymphosarcoma, there are enlarged nodes in the regions in which nodes are usually palpable, and in the mediastinum. Microscopic examination of a node removed surgically is invaluable when doubt exists. It may be remarked parenthetically that it is always important to examine patients with lymphedema carefully for evidence of malignancy.

Lipodystrophy, characterized by "fat legs," is to be distinguished from lymphedema. The characteristic symptoms which lymphedema and lipodystrophy may have in common are predilection for women, similarity in

appearance, painlessness and additional swelling of the feet or ankles when patients are much on their feet, particularly in warm weather. Lipodystrophy is uniformly bilateral, and is usually associated with generalized obesity or obesity about the pelvis. The degree, but not the extent, of lipodystrophy may progress after it is first noted. In contrast, lymphedema is usually unilateral, is not ordinarily associated with obesity and usually progresses from the foot proximally, except when it is congenital. Attacks of lymphangitis and cellulitis may occur in lymphedema but not in lipodystrophy. Pitting on pressure may occur in both conditions, but it is less evident in lipodystrophy. The diminution in size, which may follow elevation of the extremities in both conditions, is more marked in lymphedema.

The edema of deep thrombophlebitis is usually to be distinguished from lymphedema because the former is similar to lymphedema in so many respects. Well advanced stages of either condition offer little difficulty in diagnosis. The hypertrophied limb, with the thickened skin and firm consistency, characteristic of advanced lymphedema, has little similarity to the limb in cases of deep thrombophlebitis, for the latter is marked by softer edema, stasis ulcers, dermatitis and superficial varices. To be sure, when attacks of recurrent lymphangitis or cellulitis occur, the leg that was originally edematous from venous obstruction acquires an additional element of lymphedema, and lymphedema may occur around varicose ulcers as a result of chronic infection. So far as we are aware, however, pure uncomplicated lymphedema, whatever its origin, does not lead to ulceration. It is in the earlier phases of the two diseases that difficulty is encountered, the usual similarity of symptoms includes unilaterality, pitting on pressure, normal skin texture and disappearance of edema following elevation of the limb. Dissimilarities exist in the circumstances of origin, speed of onset and progress, distress experienced by the patient and condition of the superficial veins. Thrombophlebitis with edema usually occurs in the course of or following an illness such as pneumonia or typhoid fever, or follows childbirth or operation. During the acute stage, a dull aching distress occurs in the area of the involved vein, which is tender to pressure, the edema develops rapidly to its fullest extent in the course of hours, and the superficial veins are dilated and the pressure within them is increased. Lymphedema does not ordinarily occur during systemic disease. The absence of distress is striking, except when acute cellulitis and lymphangitis occur, the edema ordinarily develops to its fullest extent slowly during a period of weeks, months, or years, and the superficial veins are not dilated. Among dissimilarities, the localized distress that occurs in thrombophlebitis is most important. Occasionally, the two conditions may coexist, as in the case of the thrombophlebitic limb that is involved in recurrent attacks of lymphangitis and cellulitis. In rare instances, it may be difficult, if not impossible, to distinguish between the two conditions, although roentgenologic studies

may be of some value²⁶ The difficulty is particularly great when patients can relate only vague details about the development of the edema Further study of the disappearance of dyes injected into edematous tissues, and of the renal excretion of dyes in such experiments may aid in the differential diagnosis

MEDICAL TREATMENT

Medical treatment, in order to be of value, must be carried out early There is no medical treatment of value when the limb is greatly hypertrophied from the overgrowth of connective tissue Treatment must be instituted when the edema first becomes evident The longer uncontrolled lymphedema exists, the more fibrosis occurs, and the less efficient medical treatment becomes This point needs to be emphasized, for most of our patients who have lymphedema have had it for a long time, and marked fibrosis, which cannot be influenced by medical treatment, has already occurred

Control of Edema The rationale of attempting to control edema is based on a conception of the condition within the tissues Large lymphatic spaces exist, valves are absent or are functionless as a result of dilation of the lymph vessels, and lymph, which ordinarily moves proximally as a result of muscular activity and the action of valves, is static, or flows to dependent parts A close parallelism exists with the condition present in varicose veins The problem is one of causing the lymph to move toward the body by preventing stasis We know of no way to accomplish this medically, other than by compressing the limb by adequate bandaging An important first step is elevation of the extremity until as much as possible of the lymph has been removed from the extremity Cloth bandages are of little or no value, the support which they give is of little value Elastic stockings are unsatisfactory in many instances, for the same reason, they tend to stretch and lose their elasticity Adhesive bandages are somewhat more efficient than the previously mentioned supports The entire criteria for establishing the value of any type of support is control of edema, a support which does not prevent swelling, when the patient is active, is valueless, one which prevents swelling is adequate We prefer a pure rubber roller bandage, 3 inches wide and 15 feet long Of the three weights available, the proper one prescribed for any specific patient depends on the difficulty in controlling the edema Ordinarily, the bandage is applied over a hile stocking, beginning by making two turns about the foot, two figure-eight turns about the ankle, and progressing up the extremity to the knee The toes and part of the heel are left exposed The bandage should be removed and applied in the same manner each time, as it becomes shaped to the extremity on repeated use If it is applied too tightly, the toes become discolored, cold, and numb If it is applied too loosely, edema results Patients soon become adept at bandaging their legs efficiently The bandage should be removed at midday and reapplied over a dry stocking after the patient has rested for an hour The same procedure is repeated at night if

the patient is active. If he remains home, he may remove the bandage and elevate the leg, while sitting. Patients object to wearing the bandages because of the inconvenience in applying them repeatedly, the slight discomfort, and their unsightly appearance. This is particularly true of women, who object to the appearance of the bandaged limb. Frequently, a well-fitting elastic stocking may be used for "dress" occasions and the use of the heavier rubber bandage may be reserved for ordinary activity. It is well to point out to women that the lymphedematous leg has an abnormal appearance which the bandage increases but little, and to emphasize that uncontrolled edema almost invariably causes a gradual increase in the size of the limb. We have no information regarding how long the bandage should be worn, in some instances, it must be used indefinitely, in others,



FIG 7 Sling for elevating leg to reduce lymphedematous swelling

improvement in circulation of the lymph may occur. Once every month or so, the bandage can be left off for a day as a trial. If edema reappears, the support must be worn again.

Treatment and Prevention of Inflammation The attacks of acute lymphangitis ordinarily subside spontaneously but recovery appears to be hastened by elevation of the limb and by the application of hot moist packs. When reactions are severe, streptococcus antitoxins, such as those which are used in the treatment of erysipelas or scarlet fever, or polyvalent serums may be used. Blood serum from patients who recently have recovered from an attack of acute lymphangitis and cellulitis may be of value. We have never observed patients to whom we thought it necessary to give antitoxins or convalescent serum for an episode of acute inflammation.

Almost the entire problem, as far as infection is concerned, is the pre-

vention of attacks. Unfortunately, we have no proved way of accomplishing this. We have felt that some commercial preparations, such as streptobacterin, when administered for a long period have been helpful but we can offer no direct evidence. More logical would be the manufacture of an autogenous vaccine from organisms which have been isolated from the tissues at the beginning of the attacks. Again, we have no definite evidence that organisms can be isolated regularly during attacks or that a vaccine would be effective in preventing them. We hope that studies with animals which have lymphedema will demonstrate the value of this method. The periodic injection of a therapeutic amount of streptococcus antiserum every few weeks may be of value. Care should be taken to avoid serum reactions. Portals of entry, such as are present between the toes in the presence of trichophytosis, should be removed. When attacks of acute inflammation recur, trichophytosis should always be suspected and vigorously treated, if present.

SURGICAL TREATMENT

The necessity of surgical treatment of lymphedema is a frank admission of failure of medical treatment in those instances in which the best medical treatment has been carried out. In many instances, however, surgical treatment is necessary because medical treatment has been carried out inefficiently or not at all. Selection of cases of lymphedema for surgical treatment depends on the etiology and severity of the lesion. There is no need to perform the operation in cases in which malignancy exists or in cases in which causative conditions of greater importance than lymphedema, such as Hodgkin's disease or pelvic tumors, are present. Unfortunately, we cannot promise the patient who has mild lymphedema a great deal of benefit. The leg can be restored to normal size and to nearly normal shape, but there is no assurance that such restoration will be in any way permanent unless an adequate type of supporting bandage is worn for an indefinite period. Therefore, the more severe the case, the more one can offer in the way of relief with surgical treatment. The history of attacks of cellulitis is not a contraindication to surgical treatment, but on the other hand, one can reasonably assure patients who have had recurrent attacks of cellulitis that the frequency of these attacks will be reduced. One should, of course, not operate during an attack of cellulitis.

The immediate preoperative care of the patient should consist of rest in bed for a few days, with the affected limb elevated continuously to reduce the edema. A sling, which supports the limb at an angle of at least 45° , should be used. Diuretics, such as salyrgan, and firm bandaging may hasten the disappearance of edema. In three to six days, as a rule, the amount of lymph in the limb will be minimal which will make the surgical procedure much easier than it would have been before.

The various surgical methods which have been used for the treatment of lymphedema have been reviewed by Ghormley and Overton. The pro-

cedure used at the clinic is that which was described originally by Kondoleon and modified by Sistrunk

The actual operation should be carried out under spinal anesthesia, using a tourniquet, applied as high as possible on the affected limb and usually without the customary towel beneath it. Two incisions are made along one side of the thigh or arm, extending as high as the lymphedema, so that a long strip of skin may be excised in an elliptical manner. The amount of tissue that can be removed will depend on the width of the strip of skin between the two incisions. As much as possible should be removed in order to reduce the size of the extremity greatly. When the incisions have been made through the skin, the margins of skin to be left are undermined for a

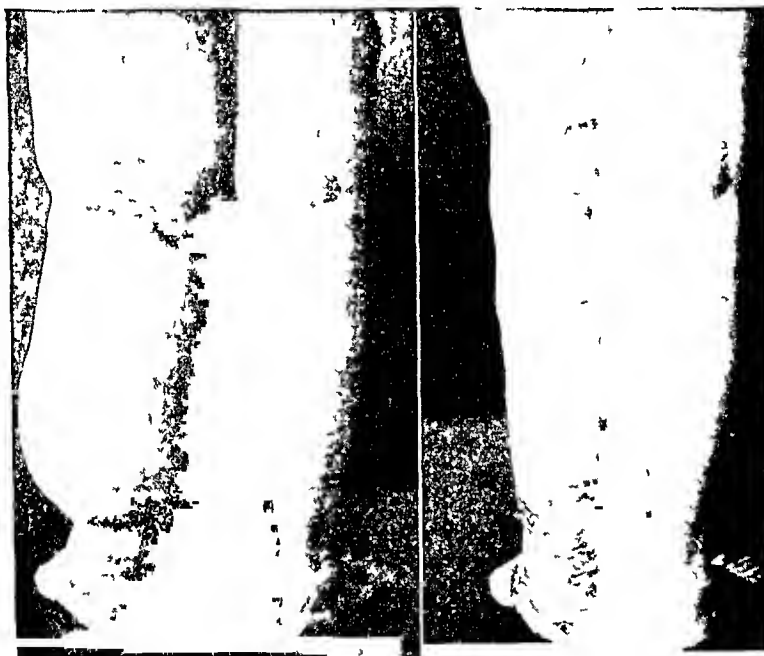


FIG 8 Appearance of limb before operation and one year following operation for lymphedema

distance on either side, approximating half of the circumference of the extremity. The skin, subcutaneous tissue, and as much as possible of fascia, except that at the intermuscular septa and at joint capsules, are removed in one piece. Care should be taken not to damage the main cutaneous nerves. After removal of the tissue, the wound should be closed with interrupted sutures. No attempt is made to secure hemostasis, only the larger branches of the veins being ligated. In closing the wound one should not hesitate to apply as much tension as is necessary, considerable tension may be applied without fear of sloughing. Indeed, it is better to have some tension than to have an excess of skin remaining redundant. A pressure bandage is applied and the tourniquet released slowly, taking

several minutes to allow the circulation actually to return to normal. We believe this step to be of considerable importance as it is possible that the sudden flooding of the circulation with material from the large wound may have had something to do with the high incidence of surgical shock. The limbs are not elevated after the operation, so that materials from the wound get into the general circulation somewhat more slowly than if the limbs were elevated. Apparently, as a result of the methods mentioned, the incidence of postoperative shock in these cases has been reduced to almost zero.

After 10 days, the dressing is changed, and if healing has advanced sufficiently, the patient is allowed to be up. Adequate bandaging, such as that described with the medical treatment, is necessary for an indefinite period. Crutches or cane are unnecessary when the patient resumes walking.

It is customary to wait from three to six months between operations. That is to say, we treat one side of an extremity and allow healing to become complete before operating on the other side. Occasionally, patients get enough improvement from the operation on one side to justify omitting the second stage, but, as a rule, a much better result will be obtained if both sides are subjected to operative treatment.

Ghormley and Overton recently have reviewed the results in 64 cases of lymphedema, in which the condition was treated surgically in the past 10 years. In 41 of these cases, there was improvement of varying degrees, no improvement was noted in eight cases, in six cases the patients had died, and in nine cases, the patients had not been traced.

Recurrent infection such as cellulitis and lymphangitis, which had been present in 25 instances preoperatively, was worse after operation than it had been before, in six cases, was improved in nine cases, and had disappeared in 11 instances, as a result of the operation.

We are not wholly satisfied with the operation described. There is considerable doubt that the benefit, which follows, results from that effect which Kondoleon originally intended, namely anastomosis of the superficial and the deep lymphatics, if, indeed, this actually occurs. Since the obstruction in many instances appears to be in the lymphatic vessels within the pelvis, little or no benefit would follow the shunting of lymph flow into the deep vessels in the leg, as these are continuous with the obstructed lymph vessels. The operation appears to us to be predominantly a plastic procedure, removing large valveless lymph spaces and hypertrophied connective tissue. As such, it is not a physiologic procedure but simply a plastic one, which corrects deformity. Since lymphedema has been produced experimentally, it is to be hoped that better methods of surgical treatment will be discovered. Perhaps the most satisfactory procedure will be found to be a combination of the plastic operation of Kondoleon and one designed to carry the lymph around the area of obstruction such as anastomosis of the lymphatic vessels of the extremity with those of the trunk. Such a procedure as the latter has been described by Gillies and Fraser.

BIBLIOGRAPHY

- 1 ALLEN, E V Lymphedema of the extremities, classification, etiology, and differential diagnosis a study of three hundred cases, *Arch Int Med*, 1934, liv, 606-624
- 2 BARKER, N W Personal communication to the authors
- 3 BARTELS, P Das Lymphgefasssystem, 1909, Gustav Fischer, Jena, 280 pp
- 4 DRINKER, C K, and FIELD, M E Lymphatics, lymph and tissue fluid, 1933, The Williams and Wilkins Co, Baltimore, 254 pp
- 5 FUNAOKA, S Der Mechanismus der Lymphbewegung, *Arb a d dritten Abt d anat Inst d kaiserl Univ Kyoto* (ser D), 1930, i, 1-10
- 6 FUNAOKA, S, and SKIRAKAWA, S Über die Entstehung der kollateralen Lymphbahnen nach Ausschaltung des Stammstroms, *Arb a d dritten Abt d anat Inst d kaiserl Univ Kyoto* (ser D), 1930, i, 15-16
- 7 GANS, O Histologie der Hautkrankheiten, Vol 2, 1928, Julius Springer, Berlin, p 177
- 8 GHORMLEY, R K, and OVERTON, L M The surgical treatment of severe forms of lymphedema (elephantiasis) of the extremities, *Surg, Gynec, and Obst*, 1935, lxv, 83-89 *Abstr*, *Proc Staff Meetings of Mayo Clinic*, 1934, xv, 564-566
- 9 GILLIES, H, and FRASER, F R Treatment of lymphedema by plastic operation (a preliminary report), *Brit Med Jr*, 1935, i, 96-98
- 10 HALSTED, W S The swelling of the arm after operations for cancer of the breast—elephantiasis chirurgica—its cause and treatment, *Bull Johns Hopkins Hosp*, 1921, xxii, 309-313
- 11 HOMANS, J Thrombophlebitis of the lower extremities, *Ann Surg*, 1928, lxxvii, 641-651
- 12 HOMANS, J Phlegmasia alba dolens and the relation of the lymphatics to thrombophlebitis, *Am Heart Jr*, 1932, vii, 415-430
- 13 HOMANS, J, DRINKER, C K, and FIELD, M E Elephantiasis and the clinical implications of its experimental reproduction in animals, *Ann Surg*, 1934, c, 812-832
- 14 HOMANS, J, and ZOLLINGER, R Experimental thrombophlebitis and lymphatic obstruction of the lower limb a preliminary report, *Arch Surg*, 1929, xliii, 992-997
- 15 HOPE, W B, and FRENCH, H Persistent hereditary oedema of the legs with acute exacerbations, Milroy's disease, *Quart Jr Med*, 1907, i, 312-330
- 16 HUDACK, S S, and McMASTER, P D The lymphatic participation in human cutaneous phenomena, a study of the minute lymphatics of the living skin, *Jr Exper Med*, 1933, lvii, 751-774
- 17 IWANOW, G Die Lymphgefasse der Wände der Blutgefasse—Vasa lymphatica vasorum sanguinorum, *Ztschr f Anat u Entwickl*, 1933, xcix, 669-685
- 18 KAPOSI, M Quoted by DORFFEL, J Histogenesis of multiple idiopathic hemorrhagic sarcoma of Kaposi, *Arch Dermat and Syph*, 1932, xxvi, 608-634
- 19 KONDOLEON Quoted by Ghormley and Overton
- 20 MASON, P B, and ALLEN, E V Congenital lymphangiectasis (lymphedema), *Am Jr Dis Child* (In press) *Abstr*, *Proc Staff Meetings of Mayo Clinic*, 1935, v, 5-6
- 21 MATAS, R The surgical treatment of elephantiasis and elephantoid states dependent upon chronic obstruction of the lymphatic and venous channels, *Am Jr Trop Dis and Prevent Med*, 1913, i, 60-85
- 22 MEIGE, H Quoted by Milroy
- 23 MILROY, W F Chronic hereditary edema Milroy's disease, *Jr Am Med Assoc*, 1928, xci, 1172-1175
- 24 OPIE, E L Thrombosis and occlusion of lymphatics, *Jr Med Res*, 1913, xix, 131-146
- 25 POLONSKAJA, R Zur Frage der Klappen in den Lymphgefassen der unteren Extremitäten des Menschen, *Anat Anz*, 1932, lxxiv, 395-397
- 26 REICHERT, F L The recognition of elephantiasis and of elephantoid conditions by soft tissue roentgenograms with a report on the problem of experimental lymphedema, *Arch Surg*, 1930, xx, 543-568

- 27 REICHERT, F L The regeneration of the lymphatics, Arch Surg , 1926, xiii, 871-881
- 28 SEQUEIRA, J H Diseases of the skin, Ed 3, 1919, P Blakiston's Son and Co , Philadelphia, 644 pp
- 29 SISTRUNK Quoted by Ghormley and Overton
- 30 TROUT, H H Ulcers due to varicose veins and lymphatic blockage, a new principle in treatment, Arch Surg , 1929, xviii, 2281-2302
- 31 WIRZ, F G M Handbuch der Haut und Geschlechtskrankheiten, Julius Springer, Berlin, 1928, viii, Part 2, 924-958
- 32 ZIMMERMANN, L M , and DE TAKATS, G The mechanism of thrombophlebitic edema, Arch Surg , 1931, xxi, 937-953

THE EXPERIMENTAL AND PATHOLOGICAL ASPECTS OF SILICOSIS :

By DUDLEY IRWIN, *Toronto, Ontario, Canada*

THE purpose of this paper is to present certain aspects of human and experimental silicosis and to report some of the recent advances in this subject, along with some of the difficulties that are being encountered by its investigators

Silicosis is an industrial disease of increasing importance that has been recognized by the clinician for the past hundred years. Formerly this condition was known by many names, such as grinder's rot, miner's phthisis and stonemason's lung. Gradually these occupational diseases were found to be associated with the inhalation of dust in the corresponding trades. The pathological lesions in these pulmonary conditions were essentially the same and from statistical data some form of finely particulate silica was thought to be the harmful ingredient in the inhaled dust. Today this condition is recognized as a type of pneumokoniosis and is known more or less universally as pulmonary silicosis.

The investigators of any pulmonary disease caused by the inhalation of silicon compounds are chiefly concerned with the extremely fine particles that gain entry to and are retained by the lung. In silicosis the majority of these particles are under three microns and very few are over five microns in their greatest diameter. The minuteness of these particles is appreciated if it is kept in mind that the diameter of a streptococcus is one micron.

The chemist can quantitatively analyze siliceous material for its constituent elements, such as silicon, potassium and aluminium. Analysts express the quantity of these elements in terms of the corresponding oxides. They therefore express the amount of silicon in terms of silica, though all the silicon may have existed in the form of a silicate, none actually being present as silica. This is misleading to the pathologist unless the significance of such an expression is borne in mind.

The mineralogist by the microscopic observation of the optical properties of small fragments of siliceous crystals can specifically identify fragments as small as ten microns. According to Knopff, particles under ten microns cannot be specifically identified by this method.

The physicist by the aid of the spectroscope or roentgen-ray absorption spectra could specifically identify the most finely particulate material if he were dealing with a single compound, but when a variety of compounds are present these methods have also failed.

This inability specifically to identify finely particulate siliceous material is a stumbling block to the investigators working on the problem of silicosis.

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935
From the Department of Medical Research, University of Toronto

It is a phase of the problem now receiving considerable attention, and from present indications may be solved in the near future

The pathologist also has his difficulties. He relies on the chemist for a quantitative estimation of the silicon present in a tissue, but he must be able to demonstrate the siliceous material microscopically in order to study any tissue reaction that may be associated with its presence

The most satisfactory method for the histological demonstration of siliceous material in tissue is that of microincineration. This consists of placing an ordinary histological section on a glass slide and heating it to a dull red until all the organic substances are removed. The inorganic material is left behind and is so remarkably *in situ* that the skeletons of single cells can be identified. This ash can be treated with aqua regia to remove the soluble chlorides without disturbing its pattern. The acid insoluble ash consists almost entirely of siliceous material. Serial sections permit the orientation of the total inorganic and the siliceous ash to the histological structures in which they were contained. This method also has the advantage of unmasking the siliceous material that is obscured in the ordinary section by carbonaceous pigment or rendered occult by hydration.

A knowledge of the amount, identity and distribution of the siliceous material that may exist in the tissues of a healthy individual is essential before silicotic lesions can be appreciated.

Recent investigations by McNally in this country, and Fowether in England, place the amount of siliceous material in the lungs of normal individuals as 100 to 200 milligrams per cent dry weight. Belt, King and I have recently investigated the amount of siliceous material in the tissues of individuals who had been exposed only to the dust present in the ordinary atmosphere and whose tissues showed no evidence of any fibrosis associated with the siliceous material present. Thirty-five tissue specimens were studied from each of six individuals coming to autopsy, the ages being from two months to 78 years. Most of these tissues were healthy but some were selected that presented pathological lesions, such as inflammation and new growth. These tissues were divided into two parts. The first was assayed chemically for the amount of silicon, which was expressed as equivalent silica. The second was cut in paraffin so that histological sections could be studied and the technic of microincineration used. This allowed a study of the amount and distribution of the siliceous material. The specific identity of the silicon compounds could not be ascertained. The amount of siliceous material in the tissues apart from the lungs was approximately 25 milligrams per cent dry weight of tissue. This amount was practically the same at all ages, and in all tissue whether healthy or diseased. Microincineration showed the siliceous material to be distributed diffusely throughout.

Particular attention was paid to the lungs and pulmonary lymphatics, as they contained large amounts of siliceous material. On this account 30 additional normal lungs were studied to enlarge the series. In the total 36

lungs we found that the amount of siliceous material was the same at birth as in the other tissues, but that there was a gradual increase until the third or fourth decade, when a level of 100 to 200 milligrams per cent was reached that more or less persisted in the later decades. This suggests that about the third or fourth decade a balance is reached between the siliceous material retained by the lung and that removed from the lungs by the pulmonary lymphatics.

The amount of siliceous material in the peribronchial and mediastinal lymphatic glands increases proportionately with the age of the individual. From the beginning of the third decade these glands contain tremendous amounts of siliceous material when compared with the other tissues, usually 2000 to 4000 milligrams per cent and not uncommonly in advanced years, 5000 milligrams per cent dry weight. These glands contain from 10 to 25 times as much siliceous material as the corresponding lung tissue and from 50 to 80 times as much as the other tissues, apart from the lungs. In these lungs and pulmonary lymphatic tissues the siliceous material was not evident in the stained sections, as it was constantly associated with and obscured by the ever-present black carbonaceous pigment. This siliceous material was demonstrated by the technic of microincineration and was found to be distributed throughout the lung and lymphatic tissue in collections of varying size. The concentration of the siliceous material in these collections was quite uniform.

These findings make several points clear. First, large amounts of siliceous material can exist in the pulmonary lymphatics for long periods without producing any pathological lesions. Secondly, the black pigment in lung or pulmonary lymphatic tissue is almost without exception a guide to the amount and distribution of the siliceous material present. Thirdly, the inclusion of peribronchial lymphatic nodes in the tissue of a lung suspected of being silicotic will give a false impression of the amount of siliceous material present.

Investigators of the pneumokonioses have been much more interested in the dust that is retained by the lung and the results produced by its presence, than in the dust temporarily held by the lung and eliminated normally in the bronchial mucus. The bronchial tree from the larynx to the respiratory bronchioles is lined by tubular escalators formed by the layer of mucus continuously propelled toward the larynx by ciliary movement. Dust particles coming in contact with this sheet of mucus are soon eliminated in the sputum.

The functional unit of the lung consists of the respiratory bronchiole and the atria and alveoli that arise from it. This structure is conveniently compared to a bunch of grapes, the main stem the respiratory bronchiole, the stem branches the atria and the grapes the alveoli.

Dust coming in contact with the alveolar walls could be eliminated by the healthy lung in several ways. It would appear that the respiratory

movement of the alveoli might physically extrude some of the dust particles. The alveolar phagocytes having engulfed dust particles might carry them to the bronchiolar mucus. The mucus of the bronchial tree is supplied by glands and goblet cells that become fewer as the periphery of the tree is approached. It is assumed that the alveoli are lined by a layer of fluid that is continuous with the fluid lining the terminal bronchioles. If such be the case, the terminal bronchioles must derive much of their fluid by pulling it from the alveoli by ciliary movement. If this hypothesis is correct, this fluid layer should be capable of removing much dust.

The failure of this mechanism of elimination allows dust that comes in contact with the alveolar walls to collect and remain in the lung. This incarcerated dust is engulfed by the alveolar monocytes, which, not being able to leave by the normal exit, collect in the respiratory bronchioles and pass through the walls of these structures to the lymphatic channels. When such a condition exists the ultimate result depends upon the amount and nature of the dust that gains access to the pulmonary lymphatics or remains in the smaller air passages.

The first and most important lesion in any pneumokoniosis is the functional failure of this mechanism of elimination. Strachan and Simson of South Africa, state that in silicosis a dry bronchiolitis is a constant feature and may be an important determining factor in the lung invasion. The pathogenesis of the failure of this mechanism is not known. It may be damaged in several ways. Chronic bronchitis of infective origin may produce marked damage. The chemical presence of certain dust particles may also produce marked damage. The particles of dust that reach the lung alveoli are so fine that their rate of solution is comparatively rapid.

Silica in the form of finely particulate quartz, when placed in the tissues, soon takes up water to form a substance that is toxic. The first action of such a substance in the bronchiolar mucus would probably cause slowing of ciliary movement. This in turn would tend to prevent proper elimination and allow a sufficient concentration of the toxic substance to produce anatomical change. In some industries irritating gases may accompany the inhaled dust. Gases such as the oxides of carbon, sulphur and nitrogen when in solution give rise to the corresponding acids.

Recently Robson, King and I subjected rabbits to an atmosphere containing a concentration of nitrogen dioxide 1 in 10,000, and of sulphur dioxide 1 in 20,000. The rabbits were exposed to this gas mixture for two hours daily five days a week. In the course of a few weeks all these animals showed diffuse lesions in the bronchial tree characterized by loss of cilia, degeneration and desquamation of the epithelium and in some cases a metaplastic change from columnar-ciliated to non-ciliated stratified epithelium. There was also a lymphocytic infiltration of the walls of the bronchial tree. These lungs did not show any nodular fibrosis. When finely particulate quartz was added to the atmosphere along with these gases, all the animals exposed for periods of 10 weeks or more showed nodular fibrosis con-

taining large amounts of siliceous material This fibrosis was first seen in the alveoli and later in the peribronchial lymphatic aggregations and mediastinal lymphatic glands Animals exposed to quartz dust alone required an exposure five times as long before similar lesions are produced

Our interpretation of these experiments was that the addition of the gas to the atmosphere quickly damaged the normal mechanism of dust excretion, and allowed the incarceration of relatively large amounts of quartz dust in the lungs in a comparatively short period

In industries where silicosis is common, certain men remain healthy for many years though exposed to the same atmosphere in which other men develop silicosis in much shorter periods It is probable that this individual susceptibility depends upon the functional activity of the mechanism of normal dust excretion by way of the bronchial mucus

It is frequently of importance to ascertain experimentally if a given dust is capable of producing silicosis There are several ways in which this may be investigated Dust can be added to tissue cultures and its effect on the behavior of the cells observed microscopically Animals can be exposed to a dusty atmosphere and the lungs examined at intervals This method most closely simulates human exposure and valuable information has been obtained by Gardner at Saranac Lake by this method Large numbers of animals are required as the exposure is necessarily long and fatal concurrent infections are numerous Kettle injects a suspension of dust in saline into a lung by means of a catheter This allows a large amount of dust to gain entry and remain in a lung where its effects may be followed The time interval is greatly lessened but infection may be introduced Sayers has studied the reaction produced by injecting dust into the peritoneal cavity The subcutaneous injection of dust provides a convenient way of following its reaction Dust injected intravenously is engulfed principally by the reticulo-endothelial cells of the liver, spleen and bone marrow, where its action may be followed It must be kept in mind that the reaction produced by a dust in the lungs may not be identical with the reaction produced in other tissues

Our knowledge is meagre concerning the tissue reaction produced by pure siliceous compounds that have been specifically identified and consist of particles of known size Silicosis-producing industrial dusts are almost always mixtures of various substances both organic and inorganic Ways of fractionating these dusts into their component parts must be found so that these components can be studied individually Most authorities agree that finely particulate sterile silica in any of its forms when present in most tissues produces a nodular fibrosis that closely resembles the lesions in a human silicotic lung

The size of the particles is very important Gardner has shown that the injection of quartz particles one to three microns in diameter will produce a nodular silicotic fibrosis in the same period of time that particles six to twelve microns in diameter produce only a foreign body reaction Banting has

not been able to produce silicotic nodules by the subcutaneous injection of quartz particles of colloidal size. It would seem that the larger particles dissolve so slowly that the dissolved silica is diluted and carried away by the lymph and blood sufficiently fast to prevent the formation of toxic concentrations. The particles of colloidal size dissolve very rapidly but represent such a minute amount of dissolved silica that it also can be removed before damage is done. In pulmonary silicosis the particles that produce fibrosis are those that are small enough to be engulfed by the monocytes and to dissolve quickly, yet large enough to give rise to an amount of dissolved silica that cannot be diluted or removed fast enough to prevent the formation of a toxic concentration.

The subcutaneous injection of finely particulate quartz results in a primary acute inflammation. The acute reaction subsides about the fifth day when the monocytes appear. These phagocytes engulf the quartz particles. The engulfed quartz particles are at first doubly refractive, but after a few weeks they lose this property, indicating their hydration. These monocytes degenerate, the degeneration coinciding with the hydration of the quartz. Other monocytes engulf this débris and in this way the amount of hydrated quartz contained in each monocyte is lessened. Eventually the monocytes contain an amount of hydrated quartz compatible with the life of these cells for longer periods. The monocytes then become arranged in groups, elongate, lose their power of motility, and take on the appearance of fibrous connective tissue cells. We have followed this reaction in many tissues and have found the reaction to be essentially the same in all tissues. Some difference of opinion exists as to the origin of the fibrous tissue in a silicotic nodule, but the recent work of Moen substantiates their monocytic origin. He was able to grow in tissue culture colonies of fibrous connective tissue cells from single monocytes.

The process of fibrosis in a silicotic lung is essentially the same. The distribution of the fibrotic areas depends on the amount of finely particulate silica retained by the lungs in a given period. If the silica dust is retained in small amounts over a comparatively long period it is removed from the periphery of the lung by the monocytes to the lymphatic glands of the mediastinum where fibrosis is first seen. As these glands are blocked by the fibrosis, subsequent fibrosis is peripheralward in the peribronchial lymphatic glands and aggregations until fibrosis takes place in the periphery of the lung itself. As this fibrosis is progressing the lymphatic drainage to the pleura transports dust to that part of the lung, resulting in fibrosis. This type constitutes the commonest form of the disease, that of chronic silicosis, requiring from five to 25 years for its development. If large amounts of silica are retained by the lungs in a short period of time the order of fibrosis seen in chronic silicosis is reversed. These cases constitute acute silicosis as seen in the lungs of abrasive soap workers reported by Chapman of Boston.

Much attention has been paid recently to the possibility that the retention of inhaled silicates might give rise to a fibrosis resembling that of silicosis. Asbestosis is a definite pneumokoniosis due to the reaction produced by the retention of asbestos fibers in the lung. Asbestos is a hydrous magnesium silicate. In the lung the asbestos fibers become hydrated and undergo partial disintegration. This change is associated with the production of fibrosis and suggests that the associated fibrosis is due to the chemical presence and not the physical presence of this silicate. It is not known whether the fibrosis is due to the dissolved asbestos or whether the magnesium is leached out leaving silicic acid which produces the damage. If such is the case, and convincing evidence has been brought forward recently by Berger, asbestosis is an indirect form of silicosis.

Sericite, a potassium aluminium silicate in the physical form of a fibrous secondary mica, has received much attention during the past two years. Its presence in silicotic nodules has been recognized by the South African workers for many years. Jones, a mineralogist, has attached great importance to its presence in silicotic lungs. Although he does not definitely so state, he strongly infers that the fibrosis of silicosis is due to the physical presence of the sericite fibers. From our experimental work we cannot say that sericite is entirely innocuous. We do know, however, that sericite can remain in lung, lymphatic, or subcutaneous tissues for periods of a year without producing anything but a foreign body reaction and shows no evidence of physical change by the tissue fluids. Fibers of sericite can be demonstrated in the pulmonary lymphatic glands of healthy individuals and are not associated with any fibrosis.

Tuberculosis is usually the immediate cause of death in silicosis. Many reasons have been put forward to explain the susceptibility of silicotics to this type of infection. The activation of quiescent lesions, an increased virulence of the organism, a more suitable medium for its growth, a blockage of the lymphatics, a lowered resistance both local and general, increased exposure to infection, have all been advanced. This is a subject in itself and can be mentioned only parenthetically here.

I have tried to present some of the conceptions of silicosis that are held by the members of the Department of Medical Research in the University of Toronto. We feel that this problem is by no means solved, and its solution will be brought about only by the cooperation of the medical profession with the chemist, the mineralogist, the physicist and the industrial engineer.

ACCESSORY SINUS INFECTION; ITS RELATION TO MASTOID AND LUNG INFECTIONS

By WILLIS F MANGES, M D , F A C P , *Philadelphia, Pennsylvania*

NASAL accessory sinus disease is one of the most important clinical subjects that we have to consider today. It is more frequently overlooked and more inadequately treated than almost any other disease of real consequence. If one reflects that every "cold in the head" is a possible attack of sinusitis, that each attack is apt to leave some little trace of its presence, increased by subsequent attacks and encouraging still other attacks, so that finally there is a chronic, permanent sinus infection, easily tolerated, a latent source of infection for all other portions of the body, then it becomes evident just how common and prevalent is sinusitis, why so little attention is paid to it in its earlier stages, and how potentially troublesome it may be.

The common cold may not be infectious in the first day or more, but in almost every case the secretions become mucopurulent within a few days. The mucous membrane of the sinuses is involved in the inflammation, as are the nasopharyngeal membranes. The virulence of the infective bacteria and the interference with drainage determine the severity of the individual attack.

The common "head cold" *initiates* the events considered here. A child does not first get bronchitis and then the head cold, nor does earache precede the head cold. Invariably, one may say, the nasopharyngeal lesion comes first.

It is important, too, to realize that the head cold quite frequently begins in infancy and recurs repeatedly through those first few years when the child is unable to make known his troubles except by coughing or crying. Probably very few children escape the experience. Fortunately, many of them escape the evil complications of ear infection or lung infection, but it is certain that the leading event or the principal element in the etiology of the majority of cases of infected ears or mastoids, of many of the acute, and of a still larger percentage of the chronic lung infections, is that first attack of common cold in the head, whether it begins in infancy or in later years.

It is well to consider both ear and lung lesions in the same paper as complications of sinus infection, because both of these structures are subject to direct invasion by infected material from the sinuses, and both complications are present frequently in the same patient. Either or both may occur with the first attack of sinusitis, or with any subsequent attack. More frequently the pulmonary complications develop gradually with repeated

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935

attacks of sinusitis. This is particularly true of the chronic lesions, such as bronchitis, bronchiectasis, and asthma.

The most common route of invasion from the sinuses to the ears is by way of the eustachian tube, and to the lungs by way of the pharynx, larynx, trachea, and bronchi. It is essentially a foreign body invasion, blown into the ear and drawn into the bronchi. This applies especially to bilateral bronchiectasis, and seems to be the best explanation of the fact that bronchiectasis is almost always maximal in the most dependent portions of the lungs, just where the majority of all kinds of foreign bodies tend to go. With sinusitis the individual, foreign, infection-bearing bodies may be very small but so numerous that sooner or later both lungs are involved.

This, of course, is not the only route. The lymph channels furnish another, as Mullin¹³ found after careful research. I also believe, as the late J. C. Wilson¹⁸ taught, that the inflammation in the nasopharynx travels by continuity into the larynx, trachea, and bronchi. It is entirely probable, too, that such extension occurs to the middle ear. Certainly, the lung lesions vary sufficiently to suggest various routes of invasion. In one, the involvement is mainly in the lymphatic structures at the roots of the lungs, in others, there is almost uniform peribronchial thickening evenly distributed throughout the lungs, others have bronchiectasis in the lower lobes, still others have more or less extensive adhesions or pleural thickening at the base, and some have definite allergic manifestations as the result of the sinus infection, and without lung changes other than emphysema from repeated attacks of asthma. Many patients with chronic lung infection occasionally have dyspnea of varying degree, because their exudate is at times more tenacious and interferes more with respiration, and particularly, with expiration. Under such conditions an erroneous diagnosis of asthma is frequently made.

The route of bacterial invasion is of relatively little importance. What matters materially is that we should all admit and recognize the sequence of events. Both experimental and clinical observations on the part of those definitely interested in the subject attest this sequence.

Cullom,⁵ in speaking of the various complications of sinus disease, said "I wish to emphasize one that has been brought home to me forcibly. I was somewhat surprised in reviewing our cases of acute mastoid abscess to find that practically all of our cases done during the last four years had empyema of one or more sinuses. There should be nothing surprising in the fact, however, when we consider that the pus draining into the post nasal space passes over the orifice of the eustachian tube. The surprising thing is that they do not all get infection of the ears."

In a more recent paper, Cullom⁶ reports that 85 per cent of more than 100 patients with mastoiditis had positive evidence of sinus disease and that in all of them there was a diseased sinus on the same side as the infected mastoid.

Fowler⁷ considers that the swimming pool and the nasal douche varieties of mastoiditis are analogous to those from sinus infection. Eighty-six per cent of Fowler's mastoid patients had positive roentgen-ray evidence of sinus disease.

Campbell² found that practically all of 150 consecutive patients with ear infection had sinus infection, which he looked upon as an etiologic factor in the production of otitis. He believes that no child has reached the age of one year without having a sinus infection.

In a later paper, Campbell³ reports the study of 130 patients with lobar or bronchopneumonia. The ages varied from three months to 90 years—only seven were adults. Evidence of sinus disease was found in all. He also noted that of this group there was also ear involvement in 80 per cent.

Keller⁹ says "The head cold is the leading causative factor in the production of acute catarrhal otitis media," and also in acute purulent otitis media.

Musser¹⁴ gives a clear picture of the sequence and relation of sinus infection and the two complications considered here when he describes "Infectious Cold." He says that the disease terminates sometimes within a few days without further symptoms, and at this time the true virus infection ends. "In most instances, however, the discharge gradually becomes more purulent and less abundant. This marks the pyogenic stage of the disease and it is in this period that sinusitis and otitis may occur. Even more serious troubles may develop, including pneumonia, either lobar or lobular." In this excellent textbook he also emphasizes the sinuses as a source of infection in chronic bronchitis and bronchiectasis.

Wasson and Waltz¹⁷ made a study of 100 children from three months to eleven years of age. Of the 93 over six months of age, 71 show the presence of sinus disease. Of the 93, 36 were two and a half years of age or less, and lung lesions were not estimated. Of the remaining 57, there was no evidence of lung disease in 22, but in 28 there was roentgen-ray evidence of non-tuberculous infection. Two had non-active tuberculosis with superimposed upper respiratory tract disease, and five had non-active tuberculosis with calcification or fibrosis. All of these children had roentgen-ray examinations of the sinuses and chest every three months, so that the diagnosis was based on a large number of examinations of each case. Seventy-one of the 93 from six months to eleven years had evidence of sinus disease. Twenty-eight of the 57 had non-tuberculous infection of the lungs. This entire group was supposed to be made up of children healthy from birth.

Quinn and Meyer¹⁶ have observed from the study of 38 cases of bronchiectasis, that as a class the patients with sinusitis were considerably younger than those without. They also found that 77.2 per cent of the patients with sinus disease had bilateral bronchiectasis. The majority of their group had no symptoms of sinusitis.

These authors conducted an interesting series of experiments, dropping

iodized oil through catheters into the posterior nares of 11 sleeping patients, and they found that in five the iodized oil went into the lungs. The significance of this result must be apparent. I dare say that all of these patients were asleep in the recumbent posture. In the prone or lateral postures, I believe the iodized oil would not have gone into the bronchi.

Pierson¹⁵ has reported two cases of pneumonia associated with fibrosis from oil deposits in the lungs in quite young children, one of whom had had oil dropped into the nose to control mucus and cough, the other had been given mineral oil by mouth for constipation. He also gives references of other such cases.

In a study of 200 patients with bilateral bronchiectasis, Clerf⁴ found that 82.4 per cent had sinus disease. I had the opportunity of studying many of Clerf's cases and I know that quite a few of them were in children. He also notes the relative infrequency of sinus disease in association with unilateral bronchiectasis, which fact refutes the argument that sinus disease results from bronchiectasis. He says that bronchiectasis is not cured by treatment of the sinus disease, but treatment of sinus disease in early chronic cough is preventive of bronchiectasis.

In an analysis of the roentgen-ray findings in 354 asthmatic patients, I¹¹ found positive evidence of sinus disease in 60 per cent. Doubtful roentgenographic evidence was not accepted and in none of the patients was the diagnosis checked by means of the injection of iodized oil. This percentage, I am sure, is too low for any such group. The most important finding in this study was the fact that 85 per cent of the patients showing evidence of sinus disease also had roentgen-ray evidence of lung changes. In a former paper, I¹² reviewed the literature up to 1930 and found 20 excellent articles, all of them expressing the idea that sinus disease is responsible for the lung changes that follow.

During the past several years it has been my custom to make at least one or two roentgenograms of the accessory sinuses of patients of all ages sent to me for study of the lungs in whom I could find no evidence of tuberculosis, but who showed evidence of other infectious processes. Sinus disease has been found in a surprisingly large number. The striking fact in most instances is that neither the patient nor the physician has had any thought of sinus disease being present. Two typical examples of this combination may emphasize this point. Recently a medical student was sent to me for roentgenographic examination of his chest because of a severe persistent cough. As there was fairly extensive peribronchial thickening rather evenly distributed throughout his lungs, I had him return for sinus study and for questioning. So far as he knew, he had never had sinus disease, but had had repeated attacks of prolonged severe cough for a number of years. One previous rhinological examination had revealed nothing. A roentgenogram of the sinuses shows a completely opaque antrum on one side. At the time, he had no subjective signs of the disease and no nasal discharge. A sub-

sequent examination shows that the maxillary antrum has drained but that there is still definite evidence of thickening of the lining membrane

Another patient, the daughter of a physician, was referred for study of the lungs and heart. Cough was excessive, and one physician thought she had a heart lesion. Her root structures were enlarged to some extent and this led me to make a study of the sinuses, which revealed a completely opaque antrum. I was surprised about a week later when I was told that a rhinologist had punctured the antrum but found no evidence of pus. A subsequent roentgenographic study showed a markedly thickened lining membrane with a small amount of air in the antrum. Obviously, it would be a mistake not to try to improve this condition.

I have also made roentgenograms to include the sinuses in all cases of mastoiditis, and again in the majority, especially of acute mastoid cases, there is evidence of sinus disease, but the subjective symptoms are all referable to the ear.

It seems quite unfortunate that sinus disease, except in the fulminating type, does not produce more active subjective symptoms. This must be the reason it is so generally overlooked, not only by the general practitioner, but also by the pediatrician, the medical consultant, the otologist, and even the rhinologist.

Certainly much depends on the early diagnosis, and since the local subjective symptoms are, as a rule, so slight, one should consider what remote signs should be thought to indicate probable sinus disease. I look upon the following as strongly suggestive signs of sinus disease: Cold in the head, running nose, especially if discharge is mucopurulent in character, post-nasal drip, *cough*, especially persistent, prolonged cough, with or without expectoration, with or without fever, any slight change in the character of the voice, such as nasal twang, hoarseness or loss of voice, repeated attacks of pneumonia, asthma, particularly in children, but also at any other age, other forms of dyspnea, earache or discharging ear, mastoid disease, headache, neuralgia, etc., and, in fact, any other condition that might be considered due to focal infection.

Complete diagnosis depends upon what the rhinologist can see by direct inspection, by transillumination of the sinuses, or by puncture or other effort to obtain the contents of the sinuses. Of even more importance is the roentgenographic study of the sinuses, if it is done properly and accurately. This also offers the best means of determining results of treatment, and the only means of obtaining a visible permanent record. Injection of iodized oil is sometimes necessary to make a positive or negative diagnosis when there is any doubt. By this means alone, very slight thickening of the lining membrane can be demonstrated. Kistner¹⁰ considers thickening of as little as one-half millimeter strongly suspicious of disease. He believes the chronic, nonsuppurative, thickened membrane type of sinusitis may be the more dangerous because it usually harbors streptococci, whereas the active suppurative type is most frequently staphylococci. Other forms of bacteria

are also found, and in all types of sinus disease he found through cultures taken at operation the following in their order of frequency and predominance streptococcus, staphylococcus, *Bacillus Friedlanderi*, *Micrococcus catarrhalis*, and *Bacillus influenzae*

Campbell finds the use of the nasoscope the most satisfactory means of making a diagnosis of sinus disease in infants. On the other hand I have confidence in the roentgenographic method, but it does sometimes require a great deal of patience, and no small amount of ingenuity, to obtain satisfactory films of frightened children. With cooperation on the part of the patient, however, the roentgenographic study is by all means the most important part of the diagnostic procedure.

Treatment, obviously, cannot be adequate in the early stages when satisfactory results should be available, unless the pediatrician, the general practitioner, the medical consultant, and all the involved specialists will regard seriously the head cold and make certain that one or more of the sinuses do not contain purulent exudate, thickened membrane, or polyps, after the cold is apparently gone. Prevention of subsequent attacks and of the chronic active stage should be the object of any plan of treatment.

Cullom says that the treatment of acute sinusitis is medical and of the chronic type is surgical. Hurd⁸ in speaking of the surgical treatment of chronic sinusitis in the patient having asthma says it must be radical if undertaken at all.

Butler and Woolley¹ in reporting the results of roentgen therapy in 450 patients with chronic sinusitis say that 36 per cent are entirely relieved, 55 per cent definitely improved, and 9 per cent show little or no improvement. I have not as yet tabulated my own cases, but can testify to the value of such treatment of the sinuses, particularly in a selected group of asthmatics. The results may not be permanent because the sinusitis may recur. The soil is not permanently changed. I am not competent to discuss the various other methods of treatment, but I am certain that there is much to be desired, and I am also certain that there are relatively few physicians who take the matter as seriously as they should at the time when something might be accomplished. It is remarkable how much improvement may follow in the lung lesions, as well as the sinus disease, with skillful attention and treatment.

I have recently had return for reexamination a group of patients, mostly children, in whom I previously found unsuspected sinus disease, when they were sent for roentgenographic study of the lungs. The invariable result has been that, when the sinuses have shown improvement, the lungs also have been more clear, and there has been definite improvement in general health. On the other hand, in those patients who show no improvement in the sinus condition, the lung lesions have progressed. Once it is established, bronchiectasis is not easily eliminated, but even so, the general health of the patient will improve if the sinus infection is improved.

Nature does sometimes cure a mastoid lesion by producing a contraction

and sclerosis in the cell structure, but for the most part, radical surgery is essential to cure

SUMMARY

Nasal accessory sinus disease is responsible for a large number of serious complications particularly in the ears and lungs, but also in other parts of the body

The common head cold or infectious cold is the first stage of the sinusitis. This period is the one in which most can be gained by proper treatment.

The various types of lung lesions suggest more than one route of invasion of the infection from the sinuses to the lungs. The infection in the middle ear is probably carried there through the eustachian tube, either by being blown in or by continuity of tissue.

Subjective symptoms are frequently absent when the sinus disease is well established, whereas the subjective symptoms of the mastoid and lung complications are usually striking and sometimes quite distressing. The subjective symptoms of the complications should be considered symptoms of sinus disease. Acute mastoiditis very frequently is associated with a diseased sinus on the same side.

Sinus disease is present in a large percentage of asthmatics.

Bronchiectasis, associated with sinus infection, is bilateral in the majority of instances. Also, a large percentage of bilateral bronchiectasis has sinus disease. Bilateral bronchiectasis is to be considered incurable. It is frequently found in childhood.

Diagnosis of sinus disease should be based on direct inspection, on roentgen-ray examination, and on symptoms of the various complications.

The early ear and lung lesions respond to proper treatment of the accompanying sinusitis.

Attention to sinus disease in its early stages is extremely important.

BIBLIOGRAPHY

- 1 BUTLER, F. E., and WOOLLEY, I. M. Roentgen therapy in sinusitis, *Radiology*, 1934, **xviii**, 528-537.
- 2 CAMPBELL, E. H. Association of acute sinusitis and acute otitis media in infants and in children, *Arch Otolaryng*, 1932, **xvi**, 829-844.
- 3 CAMPBELL, E. H. Incidence and significance of sinusitis in pneumonia, *Arch Otolaryng*, 1934, **xx**, 696-703.
- 4 CLERF, L. H. The interrelationship of sinus disease and bronchiectasis with special reference to prognosis, *Laryngoscope*, 1934, **xliv**, 568-571.
- 5 CULLOM, M. M. Disease of the accessory sinuses, *Jr Tenn State Med Assoc*, 1926, **xviii**, 309-315.
- 6 CULLOM, M. M. The association of sinus disease and middle ear infection, *Jr Am Med Assoc*, 1934, **ciii**, 1695-1699.
- 7 FOWLER, E. P. The incidence of nasal sinusitis with diseases of the ear, *Arch Otolaryng*, 1929, **ix**, 159-170.
- 8 HURD, L. M. Asthma in relation to nasal sinusitis, *Trans Am Laryng, Rhin and Otol Soc*, 1933, **xxxix**, 361-364.
- 9 KELLER, J. C. *Modern otology*, 1930, F. A. Davis Co., Philadelphia.

- 10 KISTNER, F B Chronic nonpurulent sinusitis and its clinical significance, *Ann Otol, Rhinol and Laryngol*, 1929, *xviii*, 795-804
- 11 MANGES, W F The roentgen-ray study of the pathology of asthma, *Detroit Proc Interstate Postgrad Med Assemb N Am*, 1929, 48-52
- 12 MANGES, W F The relation of sinus disease to pulmonary infection, from the standpoint of the roentgenologist, *W Va Med Jr*, 1930, *xvi*, 588-593
- 13 MULLIN, W V A review of sinus-chest infections, *Ann Otol, Rhin and Laryng*, 1932, *li*, 794-804
- 14 MUSSER, J H Internal medicine, 1934, Lea and Febiger, Philadelphia
- 15 PIERSON, J W Some unusual pneumonias associated with aspiration of fats and oils in the lungs, *Am Jr Roentgenol and Rad Therap*, 1932, *xvii*, 572-579
- 16 QUINN, L H, and MEYER, O O The relationship of sinusitis and bronchiectasis, *Arch Otolaryng*, 1929, *x*, 152-165
- 17 WASSON, W W, and WALTZ, H D The relationship of sinus disease to chest disease in children, *Radiology*, 1934, *xii*, 432-444
- 18 WILSON, J C Medical diagnosis, 1915, J B Lippincott Co, Philadelphia

BASIC POINTS IN ROENTGEN-RAY STUDIES OF LUNG ANATOMY AND PATHOLOGY ¹

By KENNON DUNHAM, M D , F A C P , and JOHN H SKAVLEM, M D ,
F A C P , *Cincinnati, Ohio*

BECAUSE of their permeability, the structure of the lungs is revealed by the roentgen-ray more clearly than is that of any other organ. On the basis of anatomical knowledge so acquired, pathological alterations may be recognized on stereoscopic films, and understood in direct proportion to that knowledge. The diagnosis of any disease is not complete unless it includes accurate localization, extent and character of the lesions. For example, the diagnosis of pulmonary tuberculosis is incomplete and almost useless when based solely on the report of tubercle bacilli in the sputum. Most important in the medical or surgical treatment of any pulmonary disease is accurate localization of the lesions, of which the first step is recognition of the lobe or lobes involved, and second, accurate orientation of the lesions within the lobes. Such localization must be based on an accurate knowledge of the bronchi and all of their divisions as they are seen on stereoscopic films. To be considered satisfactory for study, stereoscopic films must clearly show the trachea and its bifurcation into the right and left bronchus, the arch of the aorta passing over the left bronchus, the pulmonary arteries and the bronchial linear markings from apex to base of both lungs.

Descriptions of the roentgenological anatomy of the bronchi have been, in general, few and unsatisfactory. We therefore offer the following as a basis for a working classification. On the right side the bronchus to the upper lobe, given off above the pulmonary artery, is termed anatomically the eparterial bronchus. Within the upper lobe this bronchus breaks up into three main trunks. The vertebral trunk is the smallest, and extends directly upward from the top of the hilum shadow into the apex, running parallel to the vertebral column. The linear markings of this trunk all lie within the circle of the first rib. Thus a lesion limited to the apex of an upper lobe involves this area. The anterior and posterior branches of this division are so close together that it is often impossible to separate them unless a lesion is present in one or the other. Frequently a lesion in this area comes to the pleural surface along the mediastinum. The first interspace trunk, extending out from the hilum, passes outward and upward breaking up into linear markings under the pleura behind the first interspace. Thus a lesion limited to the anterior branch of the first interspace trunk will come to the surface below the clavicle. A lesion of the posterior branches of this trunk will come to the pleura just beneath the spine of the scapula. This is a very common location for an unrecognized tuberculous lesion or for the

* Read at the Philadelphia meeting of the American College of Physicians April 30, 1935

lodgement of a light weight foreign body Usually lung abscess following surgical procedures in the mouth or throat is found in the right lower lobe but often it is overlooked in the posterior first interspace trunk area of the right upper lobe The second interspace trunks are much larger and cover the greatest area in the lobe The dependent branches spread out over the entire base of the upper lobe The anterior branches end in linear markings behind the second and third interspaces, the posterior branches extend into the axilla and reach the pleura of the interlobar fissure between the upper and lower lobes

The bronchus to the right middle lobe is given off below the pulmonary artery It is visualized extending directly anteriorly from the hilum beneath the fourth and fifth interspaces After the middle lobe bronchus is given off, the right main stem bronchus continues down into the lower lobe and divides into numerous branches which extend either to the posterior base of the lobe or anteriorly toward the interlobar pleural surface To the apex of the lower lobe is given off a branch which has extremely important significance This apical branch is given off from the main bronchus directly opposite the branch to the middle lobe It courses directly backward pointing to the pleural surface under the seventh interspace posteriorly This bronchus can only be seen on stereoscopic films because it directly overlies the hilum shadow A lesion localized in this trunk area is present in the apex of the lower lobe Localization here is extremely important Too often we have seen abnormal densities in this area interpreted as being part of the hilum shadow when actually the density was produced by a pathological lesion in the apex of the lower lobe This area is frequently the site of a lung abscess Likewise in pulmonary tuberculosis it is common observation that when spread from an upper lobe lesion occurs it is likely to extend into the apex of the lower lobe The frequent occurrence of a cavity in the upper lobe together with caseous bronchopneumonia in the apex of the lower lobe is well known Recognition of involvement of the apex of the lower lobe can and should be made early

On the roentgen-ray film the left bronchus is seen curving under the arch of the aorta The bronchus to the left upper lobe is given off below the pulmonary artery and hence is anatomically given reference as an hyparterial bronchus In the upper lobe the bronchus shows the same division of vertebral, first interspace and second interspace trunks with similar distributions as in the right upper lobe But in addition there is a long branch which curves around the left border of the heart down into the lingual tip This trunk is unusually prominent in heart conditions, especially mitral stenosis The bronchus to the left lower lobe follows out exactly the same divisions and distributions as in the right lung

This division and distribution of the bronchi is demonstrated by proper anatomic dissection of lungs It is our routine procedure in performing postmortem dissection of the lungs for pathological study to follow out ana-

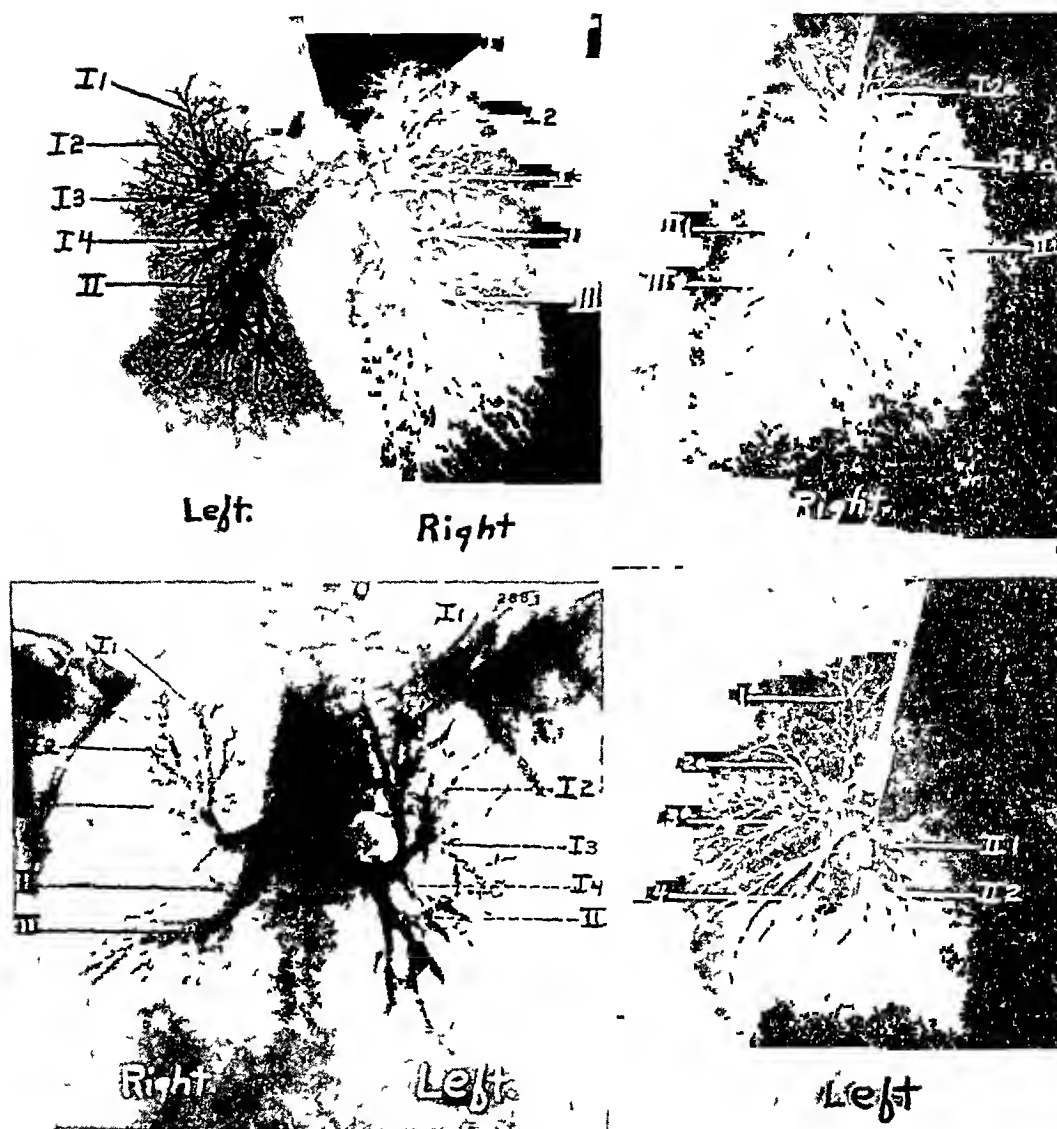


FIG 1 Roentgen-rays of injected bronchi in lungs removed from body and in a cadaver

Trunk Markings of Roentgen-Rays of Lungs

Right Lung

- I Upper Lobe Bronchus
 - 1 Vertebral Trunk
 - (a) anterior division
 - (b) posterior division
 - 2 First Interspace Trunk
 - (a) anterior division
 - (b) posterior division
 - 3 Second Interspace Trunk
 - (a) anterior division
 - (b) posterior division
- II Middle Lobe Bronchus
- III Lower Lobe Bronchus
 - 1 Apical Trunk
 - 2 Basal Trunks

Left Lung

- I Upper Lobe Bronchus
 - 1 Vertebral Trunk
 - (a) anterior division
 - (b) posterior division
 - 2 First Interspace Trunk
 - (a) anterior division
 - (b) posterior division
 - 3 Second Interspace Trunk
 - (a) anterior division
 - (b) posterior division
 - 4 Lingual Tip Trunk
- II Lower Lobe Bronchus
 - 1 Apical Trunk
 - 2 Basal Trunks

tomic dissection along the bronchi. First the main bronchus is opened and exposed in a longitudinal manner so as to show the structures at the hilum and the openings of the bronchi to each lobe. Then the bronchi are dissected by carefully slipping a small groove director into each division and with a long thin sharp knife cutting in the groove director and laying open the bronchus. In the upper lobes it is easier to open the bronchi in the lower portion of the lobe and then proceed upward. Demonstrations of these divisions of the bronchi are also made by the use of stereoscopic films of the lungs, removed from the body, in which the bronchi have been injected with an opaque substance. The specimens are prepared by injecting a thin paste of corn starch and bismuth in the trachea and bronchi of both lungs. Further demonstration of the bronchi is made by stereoscopic chest films taken of a cadaver in which the bronchi of both lungs have been injected with opaque bismuth paste. Since the advent of lipiodol injections into the bronchi the demonstration and study of the bronchi by this method have added complete confirmation of this classification and description. Furthermore from the start we have checked our roentgenographic findings accurately with the beautiful models and description of the bronchi by Birsch-Hirschfeld.¹

The extent to which thoracic viscera may be dislocated by scar tissue is well known. But often we are not able to recognize the extent to which the lobes of the lungs are disturbed. The upper lobe is often contracted and foreshortened so as to lie entirely above the second rib, or the lower lobe may be so atelectatic and collapsed as to be hidden entirely behind the heart. Compensatory emphysema in the remainder of the lung allows it to fill the thorax. These changes may lead to serious clinical mistakes as to localization and extent of lesions, mistakes obviated only by competent roentgen-ray study of the bronchi with identification of the lobes.

The trunk markings seen in chest films are interpreted as being due to the bronchi. It is true that every trunk marking represents a bronchus, but these trunk markings are not produced by the bronchus alone. They are produced by the bronchus and the pulmonary artery, together with the lymphatic vessels and connective tissues around them. The pulmonary artery at the hilum on the right side lies below the bronchus to the upper lobe and on the left side above the main bronchus as it enters the lung. The pulmonary arteries can be visualized in these positions as they enter the lungs. Certain pathological changes cause dilatation and engorgement of the pulmonary arteries with consequent emphasis of the corresponding roentgenographic densities. Notably this change is found in emphysema. The increased translucency of the lung fields, the wider separation of the trunk markings and especially the accentuation of the pulmonary arteries speak for pulmonary emphysema. Within the lung the pulmonary artery follows the bronchus in all its divisions. It occupies a position slightly posterior and lateral to the bronchus.² Therefore, any condition which causes en-

gorgement, thickening or tortuosity of the pulmonary arteries will produce thickening of the trunk markings. This is notably true in mitral stenosis, congenital heart disease, or with any failing heart with consequent pulmonary congestion. Most striking are these findings in pulmonary sclerosis (Ayerza's disease).

Another anatomical point, important to understand thoroughly in order to evaluate and diagnose pulmonary disease, is the position of lymphoid tissue and the normal lymph flow in the lung. Large collections of lymph



FIG 2 Roentgen-ray of the chest of a case of congenital heart disease showing enlarged and thickened pulmonary arteries on both sides. Relationship to main bronchi is shown.

nodes are present at the bifurcation of the trachea and also in the hilum. Within the inner third of the lung, true lymph nodes are found along the bronchi in the angle at a bifurcation. Beyond the inner third of the lung we continue to find collections of lymphoid tissue but not anatomical nodes. In the lower lobes, however, the larger lymph nodes are found along the bronchi farther out than the inner third zone. Therefore, the trunk markings running into the lower lobes are normally heavier, are more studded,

and frequently more calcified. It is easy to overemphasize the significance of these studded heavy trunk markings. In such a condition as pulmonary Hodgkin's disease, a knowledge of the normal location of lymphoid tissue is of great aid in detecting the abnormal. The normal lymph flow in the lung is from the periphery of the parenchyma toward the hilum, except for a narrow zone beneath the pleura where the lymphatics about the veins drain toward the pleura. Infection is not carried by the lymphatics from the hilum out into the lung. Infection is carried by the lymphatics from the lung to the hilum. The bronchi, pulmonary arteries and pulmonary veins all have a rich supply of lymphatics accompanying them. Any acute respiratory infection, especially the exanthemata of childhood, may leave in its wake thickened trunk markings and enlarged pulmonary and hilum lymph nodes. The clinical significance of such findings in a child is of such importance as to have been the subject of a special investigation by a committee of the National Tuberculosis Association,³ in order to standardize the interpretation. The report of this committee included the following paragraph:

It was the consensus of opinion that children are probably more apt than adults to show definite x-ray evidence in the hilum and trunk shadows of simple as well as serious respiratory infections. Practically all children of the ages of those examined have had at one time or another one or more respiratory infections, especially measles, and whooping cough, that are likely to produce very apparent changes in the shadows mentioned and which will remain distinctly visible for a variable period of time. These apparent deviations from the normal are not necessarily abnormal when observed, but may be the harmless results of one or more infections. No doubt such appearances have many times been misinterpreted as evidence of tuberculosis.

The primary lobule, as described by William Snow Miller,² is a microscopic unit of the lung. Yet a thorough understanding of this anatomical unit, its structure and physiology is absolutely necessary for an accurate study of lung diseases. In consequence this unit must be brought into the mental picture when making a visual dissection and interpretation of lung disease by roentgen-ray examination. The primary lobule is that terminal division of the bronchus which includes the ductulus alveolaris and the air sacs connected with it, together with their blood vessels, lymphatics and nerves. At the end of the ductulus alveolaris, where the division into atria takes place, is the last point where we find lymphoid tissue and lymphatic vessels. Beyond this point in the atria, sacculae alveolaris, and alveoli, foreign material, organic or inorganic, is taken up and handled by the phagocyte. Any foreign invader, be it coal pigment or tubercle bacillus, which penetrates to this depth of the lung structure is engulfed by the phagocyte and deposited in the regional lymphoid tissue. Marked accumulation of phagocytes constitutes an exudate which may flood the alveoli and give the picture of pneumonia. This primary concept of inflammation in the anatomical unit is basic for diagnosis and study of lung disease by any method. Another point of interest and clinical significance is the arrangement of

smooth muscle at the end of the ductulus alveolaris. Here the smooth muscle ends in a thickened circular sphincter-like ring². It seems logical to us to assume that in bronchial asthma with expiratory stridor the narrowing of the breathing tube takes place at this point where the sphincter-like muscle is present. This deduction awaits confirmation when studies of nerves and ganglia in the lung are more complete. We find some reason to attribute such action to this band of muscle because of our findings with lipiodol injections in pulmonary emphysema. In a normal lung, when lipiodol is injected into the bronchi and films taken immediately afterward, the air sacs are seen to be filled with the opaque oil and a rosette-like picture is given to the termination of the bronchi. In emphysema, however, the air sacs remain unfilled and the terminations of the bronchi stand out sharp and tapering. This observation is in direct contradiction to the findings and explanation of certain investigators in England. However, after checking this observation for three years, we are more and more impressed with its significance. Our deduction is that, as in bronchial asthma, the sphincter-like muscle narrows the entrance to the terminal air sacs and so impedes the entrance of the oil.

The secondary lobule is an arbitrary unit of the lung, accepted as being the amount of lung contained between two septa. These units, while they may be macroscopic, are not seen roentgenographically. Yet their influence on pathologic alterations in the lung is so great that a consideration of them is imperative. It is because of septa that sharply localized lesions are so often seen. Septa are prolongations of connective tissue from the pleura down into the lung. This connective tissue, rich in lymphatics, acts as an excellent barrier to the spread by continuity of any lung disease characterized by exudation. Inflammatory exudation, starting within any one of these small compartments between two septa will be definitely limited by these barriers. Spread through a septum will not take place until ulceration and cavitation occur. The restriction and localization of exudate by these septa explain the localized fan shaped densities on films in cases of pulmonary tuberculosis. The cellular elements of an acute lobular pneumonia or of an infarct are likewise held in check by these septa and consequently can give limited roentgenoscopic densities. Pulmonary new growths, however, are not checked by the septa, but continue to enlarge peripherally unrestrained by such barriers. Consequently the roentgen picture of pulmonary new growths is fundamentally different from that of inflammation.

The normal pattern of pulmonary anatomy having been established for roentgenoscopic study, it should be easy to recognize the abnormal. But to be able correctly to interpret the abnormal densities on chest films in terms of pathologic changes calls for understanding of the pathology and pathogenesis of lung diseases. Of prime importance are the fundamental pathological histologic changes that occur in the lung. These are congestion, exudation, infiltration, fibrous proliferation, caseation, calcification ul-

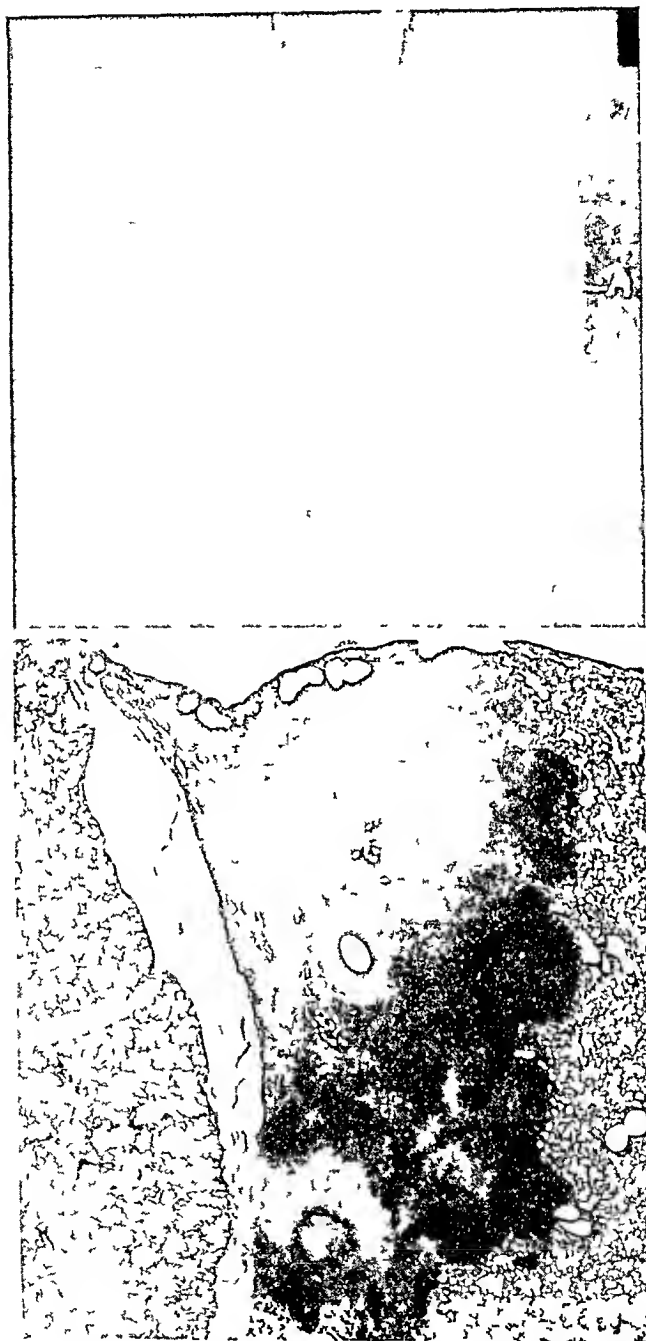


FIG 3 *Above* Roentgen-ray of the lungs of a case of pulmonary tuberculosis *A* Triangular shaped localized density seen on roentgen-ray lung films indicating caseation
Below Microscopic section through block *A* showing tuberculous caseous bronchopneumonia occupying a whole secondary lobule limited by septa



FIG 4 *Above* Roentgen-ray of the lungs of a case of mitral stenosis showing general thickening of all bronchi. *A* Limited density beneath diaphragmatic pleura indicating exudate and infiltration

Below Microscopic section through block *A* showing hemorrhagic infarct limited by septa

ceration, and cavitation. Accordingly it is necessary to determine the type and quality of density produced on a film by each of these changes. This has been done by years of observation. The interpretation of the abnormal densities seen on chest films and on films taken of lungs removed from the body, has been carefully checked by postmortem studies. The procedure for the postmortem studies is to remove from the body the lungs and trachea intact. After removal, the lungs are inflated to normal size and stereoscopic films are then made of them. These films are then studied and the interpretation recorded. The lungs are properly fixed and preserved for later gross and microscopic pathological study. In the earlier work serial sections of various types of lesions in tuberculous lungs were made for an accurate study of pathological anatomy, as a check on the roentgen-ray findings. At the Hamilton County Tuberculosis Sanatorium it still remains a routine procedure to preserve and study all lungs after this method. The gross dissection of the lungs is made along the bronchi as previously described in order accurately to localize the lesions in relation to the divisions of the bronchi. The gross pathological findings are recorded and representative blocks of tissue are removed for microscopic studies. The microscopic pathological diagnosis is then added to the record. Finally we have the clinical history and findings, the chest films, the postmortem lung films, and the gross and microscopic postmortem findings all recorded for critical review. The films have all been interpreted in terms of anatomical localization and pathological changes. The check-up is precise. During the 20 years of such study, although most of the material has been that of pulmonary tuberculosis, we naturally have encountered many examples of other chronic lung inflammation, such as abscess, bronchiectasis, fungus infections, syphilis, and new growths. These studies have taught us that the quality of the densities on the films produced by the various tissues and their abnormal changes, vary from the least to the heaviest quality as follows: 1 Cavity 2 Normal lung parenchyma 3 Exudate 4 Cellular infiltration 5 Fibrous proliferation or scar tissue 6 Caseation 7 Calcification. These comparative values of roentgen-ray densities and pathological histologic changes in the lung constitute the ground work for study of lung pathology.

The etiological diagnosis of the alterations visualized and described in the lungs must needs be amplified from our knowledge of the pathogenesis of the various lung diseases. It is of course, obvious that roentgenoscopy has distinct limitations in the exact etiological diagnosis of diseases. Lobar or bronchopneumonia can be diagnosed and localized with accuracy in terms of pneumonic exudate but the causative organism must be determined by clinical laboratory methods. Abscess or bronchiectasis can be demonstrated but the diagnosis must be completed by bacteriological and clinical studies. It must be remembered also that each or both of these conditions may be concomitants of other lung diseases such as new growths, gumma, pneu-



A



FIG 5 *Above* Roentgen-ray of the lung of a case of pulmonary tuberculosis *A* Interesting area along diaphragmatic border showing three differing densities. The heaviest zone represents caseation. The middle zone is comparatively normal. The third zone represents exudate.

Below Microscopic section through block *A* showing three distinct tissue changes. The heaviest change represents caseous bronchopneumonia, in the middle is seen normal lung, on the other side is seen acute bronchopneumonia.

As previously described, the early exudate is walled in by the septa of the lung which produces the localized fan shaped densities seen on films. This form of pulmonary infection spreads by bronchogenic or so-called intracanalicular route. In general, the course of tuberculosis is apt to be intermittent with periods of exacerbation and remission, which correspond to recurrent discharges of infection. The pulmonary lesions of an adult type are the result of repeated infections either exogenous or endogenous. This leads to multiple lesions in the lungs in different stages, of progressive and changing character. Each lesion produces a corresponding characteristic density on the roentgen-ray film depending upon the histological structure of the lesion, exudative, caseous, fibrotic or calcified. Thus on the films one may visualize densities of variable quality and by proper interpretation piece them together into the dynamic pathological picture of pulmonary tuberculosis. Lymphohematogenous or post-primary type, recently so thoroughly reviewed and brilliantly emphasized by Dr. James Alexander Miller,⁶ is graphically recorded in localization and pathological changes in terms of exudation, proliferation, fibrous tissue and calcification. Miliary tuberculosis is understood and recognized by its uniform distribution of characteristic small lesions. The basal types of caseous lobar or bronchopneumonia offer the greatest difficulty of diagnosis. The pathologic changes can be recognized but the etiological diagnosis is uncertain. Such types are particularly frequent in the negro and in that race should be more often suspected. Serial stereoscopic chest films in pulmonary tuberculosis stand as a record of the progressive pathologic changes and offer an opportunity to study, and accurately to diagnose the pathogenesis of the disease.

SUMMARY

By study of stereoscopic chest roentgenograms, the normal and pathological anatomy of the lungs can be visually dissected. Most important in the medical or surgical treatment of any lung disease is complete and accurate localization of the lesions. Localization of the lobes and lesions is made possible through accurate knowledge of the bronchi and all their divisions. The position of blood vessels and lymphoid tissue must be considered and applied in roentgenoscopic studies of the lungs. The part played by the anatomical units of the lung in the pathological changes of disease must be understood. All of these factors which make up the normal stereoscopic pattern, influence the recognition of the abnormal densities. The interpretation, however, of these abnormal densities in terms of tissue changes, demands an understanding of the pathology and pathogenesis of lung diseases. The quality of the roentgenoscopic densities produced by the various tissues and their abnormal changes are described. Pulmonary tuberculosis in its various forms can be studied and diagnosed with great accuracy by means of stereoscopic roentgenograms. The progress of the disease either toward healing by absorption of exudate, formation of fibrous scar tissue,

or spread of exudate and destruction of lung by ulceration and cavitation is demonstrated. A method of accurate control of the roentgenoscopic diagnosis by pathological studies is described.

REFERENCES

- 1 BIRSCH-HIRSCHFELD, F V Concerning the position and the development of lung tuberculosis, *Deutsch Arch f klin Med*, 1899, lxiiv
- 2 MILLER, W S Anatomy of lungs, *Reference Handbook of the Medical Series*, Vol VI, 1916, Wm Wood, New York
- MILLER, W S Some essential points in the anatomy of the lungs, *Am Jr Roentgenol*, 1917, iv, 269
- MILLER, W S Studies on the normal and pathological histology of the lungs, *Am Rev Tuberc*, 1925, xi, 1-8
- MILLER, W S The vascular supply of the bronchial tree, *Am Rev Tuberc*, 1925, xi, 87-94
- 3 Committee of National Tuberculosis Association Clinical and x-ray findings in the chests of normal children, *Am Rev Tuberc*, 1922
- 4 GHON, A Primary lung focus of tuberculosis in children, 1916, J and A Churchill, London
- 5 RANKE, K E Die primäre Lungentuberkulose des Menschen, *Deutsch Arch f klin Med*, 1916, cxix
- 6 MILLER, J A Pulmonary tuberculosis as a part of a systemic infection (hematogenous pulmonary tuberculosis), *ANN INT MED*, 1934, viii, 243-257
- 7 DUNHAM, K Localization of pulmonary lobes by the x-ray, *Med Rec*, 1920, xcvi, 1077
- DUNHAM, K X-ray examination of the chest and an x-ray classification of pulmonary tuberculosis, *Am Jr Roentgenol*, 1921, viii, 427
- 8 DUNHAM, K, and SKAVLEM, J H Comparative study of the pathology and x-ray densities of tuberculous lung lesions, *Am Rev Tuberc*, 1921, v, 278
- DUNHAM, K, and SKAVLEM, J H X-ray observations of the pathogenesis of pulmonary tuberculosis, *Tubercle*, London, 1924, v, 217-232
- DUNHAM, K, and SKAVLEM, J H Applied pathology of pulmonary tuberculosis, *Radiology*, 1925, iv, 181-187
- 9 SKAVLEM, J H Description and demonstration of anatomical dissection of lungs with practical considerations in clinical and x-ray studies, *Trans Nat Tuberc Assoc*, 1934
- SKAVLEM, J H Applied anatomy of the lungs, *Med Bull Univ Cincinnati*, 1924

CARDIAC OUTPUT IN COMMON CLINICAL CONDITIONS, AND THE DIAGNOSIS OF MYOCARDIAL INSUFFICIENCY BY CARDIAC OUTPUT METHODS *

By ISAAC STARR, JR., and C. J. GAMBLE, *Philadelphia, Pennsylvania*

THE heart is an organ with but one function. Its function is to pump the blood, it does nothing else. For this reason we have a clearer understanding of the heart than of any other organ. We can make pumps, but who can manufacture a working model of any other viscus? One can consider the heart's function in much the same way as one would consider the performance of any man-made pump.

There is no need to present the details of the methods available for measuring the amount of blood pumped by the heart, the cardiac output. All these methods are too technically difficult for general utility. There is no satisfactory way of estimating their absolute accuracy, so it is safest to regard them as inaccurate. When the better methods are applied to patients the standard deviation of duplicates from the mean is about 10 per cent^{14, 19}. But this is not cause for too much pessimism. Not long ago the different methods gave a totally different average level of cardiac output, and repeated estimations on the same subject were most divergent. Now we are far past that stage. Numerous series of normal young adults in the basal condition, examined by a number of the best modern methods, have been reported. Although these methods differ profoundly in construction and technic the averages obtained by each agree surprisingly well. The agreement of duplicate estimations has been greatly improved also. We have come a long way. Perhaps, compared to the accuracy of the data on which clinicians must base their decisions, we are not so badly off.

The time has come when clinicians should have a working knowledge of the results these methods are yielding. For either cardiac output and cardiac work are of fundamental importance, or our present conceptions of many diseases of the heart and circulation are completely erroneous. Therefore it is of interest to collect and survey the trend of results secured by the methods most worthy of confidence. One must discard from such a compilation a large number of results obtained by methods whose accuracy, in the light of modern knowledge, is doubtful. It is also safer to exclude the results secured by certain investigators who, though they used a satisfactory method, did not give satisfactory evidence that they had mastered the difficult technic. It also seems better to omit results obtained by methods which, while probably accurate enough in themselves, so disturb the subject that it seems probable that the apprehension, excitement, or actual pain en-

* Read at the Philadelphia meeting of the American College of Physicians, May 2 1935

tailed would change the cardiac output of certain patients from the true basal level

RESULTS OBTAINED BY CARDIAC OUTPUT METHODS

The data which have been included may be divided into three groups first, the results of studies of the cardiac output of normal persons, second, the results secured in clinical conditions common enough to provide a respectable series of cases, and last, the results in the less usual types of disease in which only a few, or perhaps only a single subject has been available for testing

First let us consider the results obtained on normal individuals. They may be summarized as follows:

(1) There is a definite level of basal cardiac output characteristic for each subject and analogous to the basal metabolic rate. This level is roughly related to the size of the subject^{6, 10}. Some subjects have a very constant basal cardiac output, others are much more variable¹⁰.

(2) Like the basal metabolic rate the basal cardiac output is elevated in adolescence and apparently tends to decline after 50 years of age¹⁰.

(3) The average cardiac output in the standing position is somewhat smaller than that in the horizontal position. The sitting position gives an intermediate result^{1, 4, 10}.

(4) The cardiac output is raised from the basal level by taking food, by drinking large amounts of water, by exercise, and by excitement^{2, 6, 17}. Extremes of environmental temperature will alter it also^{2, 6, 13, 17}. Note the similarity between the situations mentioned in the foregoing statement and those long known to induce attacks of angina pectoris.

Before discussing the results obtained in disease it should be pointed out that cardiac output methods yield erroneous results on certain types of patients. This must be explained in more detail.

The best of the modern cardiac output methods are based on the inhalation of gases foreign to the body and gaseous equilibrium between the lung air and blood must take place or the results will be in error. This equilibrium can be demonstrated to exist for normal persons, but when the lungs are primarily diseased, or secondarily affected by cardiac decompensation, there is a strong possibility that it may not take place. Furthermore adequate mixing of inhaled gases, required by some methods, cannot be assumed when the lungs are abnormal. Therefore workers in this field have to make a choice. Either they avoid the field of pulmonary disease altogether, or they attempt to demonstrate the principles fundamental to their method in the diseases in which they are interested. The difficulty with the latter procedure is just this: no two patients ever being exactly alike, the demonstration that the method is applicable should really be made on every patient. But when one deals with single experiments the inherent errors are so large and so hard to evaluate that, in a certain proportion of cases, they might readily yield results providing a false sense of security. Therefore,

while interesting work is being done in this difficult field we do not hesitate to say that we have not full confidence in the results obtained and, therefore, they will be omitted from further consideration at this time

The results obtained in clinical conditions, without pulmonary involvement, and common enough to permit securing a considerable series of subjects, will be considered first. Let us pay attention only to the average of the results, for this will go far towards making unimportant the inaccuracies of method, and minimizing the effect of the random fluctuations so often seen in patients. Therefore in compiling table 1, the averages only have been used. The figures can be found in the literature, we wish only to call attention to their trend

TABLE I

Clinical Conditions in Which Considerable Data Are Available

Average basal cardiac output per min. related to body weight or surface

<i>Increased in</i>	{	Hyperthyroidism ^{2 6 19 21}
	{	Anemia ^{2 6 19 21}
	{	Fever (experimental) ^{2 6 12}
<i>Essentially unchanged in</i>	{	Intercurrent disease not affecting the heart or circulation ¹⁹
	{	Hypertension ^{2 6 19}
	{	Hypotension ¹⁹
	{	Angina pectoris (between attacks) ^{19 20}
	{	Coronary thrombosis (after recovery from acute symptoms) ^{19 20 21}
	{	Valvular heart disease (when well compensated) ^{6 19 20 21}
<i>Diminished in</i>	{	Auricular fibrillation (when well compensated) ^{19 20}
	{	Cases recovered from cardiac decompensation ^{18 19}
	{	Neurocirculatory asthenia ^{18 19}

As is shown in table 1, the average cardiac output is definitely increased in hyperthyroidism, anemia, and in fever induced experimentally by typhoid vaccine or diathermy. There are no adequate data on the cardiac output in the febrile diseases.

The average cardiac output is unchanged in both hyper- and hypotension. It is unchanged in the common non-febrile diseases, diabetes, neoplasms, neuroses, gastric ulcer, etc., as would be expected. More surprising is the fact that it remains normal in the presence of certain serious diseases of the heart indicated in table 1.

On the other hand the average cardiac output is diminished in patients who have once suffered from congestive heart failure even though they have recovered from decompensation when the test is made. This result is consistent with clinical knowledge that recovery from decompensation is not complete. More unexpected was the finding that the average cardiac output in neurocirculatory asthenia was distinctly subnormal. The many symptoms which these patients share with those having serious cardiac disease may well have a common origin in this diminished circulation.

The trend of the results, obtained in conditions either rarer clinically or more difficult to secure for an estimate of cardiac output, are given in tables 2 and 3. Because of the instability of the cardiac output of certain subjects and the large errors still inherent in the best methods, we have no

confidence in the results of single estimations and have not included data of this kind. The disease conditions shown in tables 2 and 3 have been studied well enough to deserve attention, although we are by no means sure that further work will show them to be truly representative of the groups to which they belong. The number of patients tested in each group is given in brackets following the data. It is to be emphasized that this number is often very small.

TABLE II

Acute Clinical Conditions in Which but Few Data Are Available

(The change recorded is in relation to the value obtained during the patient's more normal periods. The bracketed figure gives the number of cases studied in each instance.)

Basal cardiac output per min. related to body weight or surface

<i>Increased in</i>	Acidosis (experimental) ¹⁹ (1)
	Angina pectoris (during attack) ²⁰ (3)
	Arteriovenous anastomosis (the comparison is with data obtained after occlusion of the anastomosis manually and by operation) ⁸ (1)
<i>Diminished in</i>	Artificial pneumothorax (certain cases) ³ (2)
	Paroxysmal auricular fibrillation (during attack) ¹⁹ (1)
	Paroxysmal auricular tachycardia (during attack) ^{18, 19} (3)

Table 2 shows the trend of the results in certain acute clinical conditions which, either because they were not permanent, or because they were brought about by the observer, permitted tests to be made on the same patient both in the abnormal and in the more normal condition. Therefore the change recorded is in relation to the same patient's more normal periods.

These data (table 2) deserve brief comment. The results obtained in angina pectoris indicate that increased cardiac work is an essential feature of the attack in the patients studied. This is consistent with the conception that this increased work, by creating a demand for blood which diseased vessels cannot supply, results in anoxemia of cardiac muscle which causes pain. Were angina pectoris caused primarily by spasm of coronary arteries one would expect that cardiac output would be unchanged or diminished during the attack. But the paucity of data and the difficulties of getting satisfactory estimations of cardiac output under conditions of cardiac pain must be emphasized. These patients described their pain as an ache. No estimations of cardiac output have been reported during the agonizing pain characteristic of the more spectacular forms of angina.

While careful work has demonstrated that in certain cases artificial pneumothorax is followed by a reduced cardiac output, in other cases no change has been demonstrated.

Paroxysmal tachycardia was accompanied by a marked diminution of cardiac output in three cases, but in one case, in which duplicate estimations were not made, no change was detected.

Table 3 gives the trend of the results in more permanent conditions, and the change indicated is in relation to data obtained in normal persons. The field covered is extensive, and limitation of space permits emphasis of only a few points.

TABLE III

Chronic Clinical Conditions in Which but Few Data Are Available

(The change recorded is in relation to data obtained on normal persons The bracketed figure gives the number of cases studied)

Basal cardiac output per min related to body weight or surface

<i>Increased in</i>	{ Aortic regurgitation (well compensated) ^{1 5 19 21} (8)
	{ Coarctation of aorta ⁷ (1)
<i>Essentially unchanged in</i>	{ Addison's disease (not in shock) ^{19 20} (3)
	{ Aortic regurgitation (well compensated) ^{1 5 19 21} (12)
	{ Portal cirrhosis of liver ^{19 20} (2)
	{ Acute endocarditis ¹⁹ (5)
	{ Heart block (congenital) ² (1)
<i>Diminished in</i>	{ Advanced mitral stenosis (well compensated) ²¹ (4)
	{ Aneurysm of the aorta ^{19 20} (6)
	{ Auricular flutter ²⁰ (1)
	{ Heart block (acquired, complete) ¹⁹ (2)
	{ Hypertension (certain cases with small hearts) ^{18 19 20} (8)
	{ Myxedema ^{19 20} (2)
	{ Pick's syndrome ^{11 21} (5)

The increased cardiac output found by four authors in certain cases of well compensated aortic regurgitation is unexpected enough to deserve attention. Perhaps it should be thought of in connection with the demonstration by Sir Thomas Lewis⁹ that peripheral vasodilatation is present in certain cases of this disease. If there is general vasodilatation and the blood pressure remains unchanged, an increased cardiac output becomes a logical necessity, and these results are a demonstration of this point of view. But it must be remembered that only about one-half of the reported cases show this increase.

The diminished cardiac output found in certain cases of hypertension demonstrates a type of compensation which needs emphasis. By reducing its output the heart can maintain a high blood pressure without doing more work than normal. This is doubtless the reason for the absence of cardiac hypertrophy in certain cases of hypertension. Most cases of hypertension have enlarged hearts and, the cardiac output being normal, the heart's work is increased.

ON THE DIAGNOSIS OF MYOCARDIAL INSUFFICIENCY

Now let us leave the field of description and ask ourselves some questions concerning the possibility of diagnosing myocardial disease by means of cardiac output methods. At first thought one would expect that patients with bad heart muscles would have a smaller cardiac output than normal persons. But the problem turns out to be far more complicated than this. Most workers in this field are agreed that the basal cardiac output, related to the patient's weight, or surface area, cannot be used to decide whether an individual's heart muscle is diseased or not. Although the averages differ, many individuals with every evidence of serious myocardial disease have cardiac outputs which are at or even above the normal average. Obviously the body bends every effort to maintain the cardiac output at a level sub-

servient to the body's needs. If we are some day to use these methods to detect myocardial disease we must look elsewhere than at the basal cardiac output per minute referred to the size of the body.

Our problem, therefore, is first to understand myocardial disease, when we understand it thoroughly, its detection should be easy. One can think of the heart as a pump and, to get the problem clearly before us, let us consider a simple man-made pump standing over a well. Were such a pump to perform badly, and were one to apply medical methods of diagnosis, one would listen learnedly over the valves with a stethoscope, and would attach wires to various parts and attempt to draw conclusions from the deflections of a galvanometer, the "electropumpogram." But certainly these methods would leave much to be desired and all of us would proceed more directly to quantitative measurement. Our first thought might be to measure the length of time it would take to fill a bucket with water, to ascertain the normal output, and to compare the performance of our pump with it.

But there are difficulties with this simple method of procedure. A man comes to his well, and labors with the pump handle as usual, but he is rewarded by a miserable trickle of water. He suspects that the pump is out of order. He is entirely wrong. The well is going dry. The pump cannot function unless water is conducted to its inlet, neither can the heart pump blood unless the latter is delivered to it by the veins. A small output is not compelling evidence either of a broken pump or a diseased heart. The profession has often gone wrong on this point. When, in acute infection, the circulation begins to fail how often has our therapy been directed at the pump whereas the trouble is more often analogous to the well going dry.

One other fundamental conception can be best explained by another homely example. Our friend attaches the garden hose to his pump. While he puts his usual effort into the handle, his wife, to play the stream upon the farthest flower bed, tightens the nozzle. Now the stream squirts higher and farther than before, but it has been reduced in volume, it takes longer to fill the bucket, the pressure has increased, the output decreased. Therefore the pump's output is in part dependent on his wife's adjustment of the nozzle, and the cardiac output is likewise in part dependent on changes in the caliber of the arteries. But, as long as he labors with constant effort on the pump handle, one attribute of the flowing stream is practically independent of his wife's adjustments, this is the product of output times pressure, i. e. the work. His wife has it in her power to increase the pressure, but in so doing she diminishes the output, the product, output times pressure, remains the same, no matter how she adjusts the nozzle, within reasonable limits. Similarly changes in the peripheral circulation can change the output, but the work is a function of the heart alone. Obviously the work of the heart is more likely to be of service in indicating the heart's condition than is the output.

Let us next consider the behavior of the heart under certain experimental conditions analogous to those which have been mentioned. The late Pro-

fessor Starling devised an animal preparation for studying the heart and the experiments were first performed by him and his associates¹⁶ Figure 1 shows a typical result You constrict the out-flow tube Suddenly meeting increased resistance the heart fails to empty as completely as before The same amount of blood flows in during diastole, the chamber enlarges and the muscle fibers are stretched and, like other stretched muscles, the heart begins contracting with more vigor, the circulation is restored with the heart larger and working harder than before

If, on the other hand, one constricts the inlet tube the heart does not fill

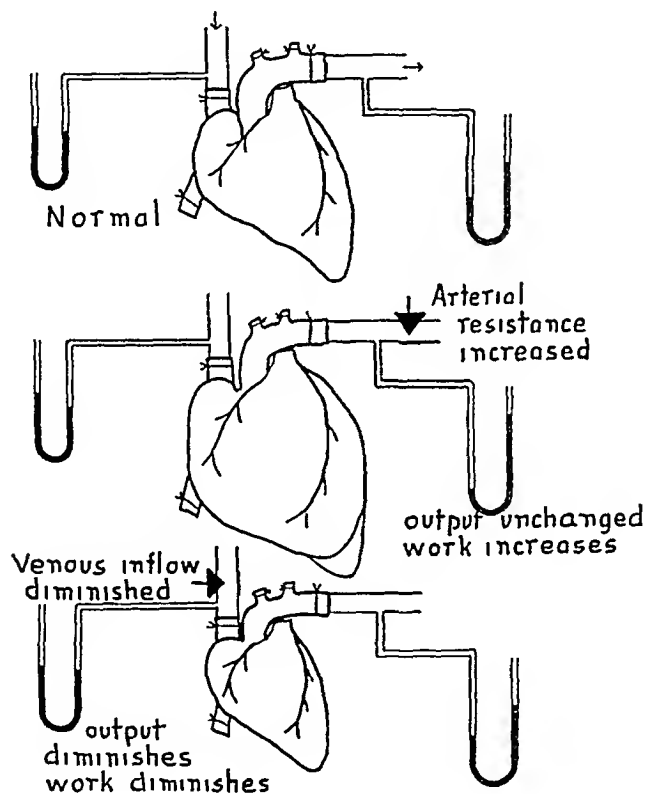


FIG 1 "The work of the normal heart per beat is a function of its size" Diagram illustrating the type of evidence on which Starling's "Law of the Heart" was based To avoid confusion, the lungs and the other apparatus essential to Starling's Heart-Lung Preparation have been omitted

as well during diastole It therefore gets smaller and when equilibrium is attained we have a smaller heart doing less work Starling pointed out that under all these conditions the work of the heart per beat was proportional to its size and this principle has since been known as Starling's "Law of the Heart" When the heart begins to fail the law does not hold, for the heart gets larger instead of smaller as its work decreases

Now by means of cardiac output measurements and the ordinary blood pressure estimations one can roughly estimate, in patients, the largest part

of the heart's work, that performed by the left ventricle. The size of then hearts can be estimated by roentgen-rays, preferably using the orthodiagraph. One can calculate left ventricular work per beat and heart volume and see where the results lead.¹⁹

We have a series of well over 250 cases^{19, 20}. One can separate out a group characterized by the fact that there is no suspicion of cardiac disease in any. Otherwise they are very divergent, including normal persons, persons suffering from diseases not affecting the circulation primarily—tumors, neuroses, diabetes, etc. Also those with diseases affecting the circulation but not, in the instances chosen, the heart—hyperthyroidism, anemia, hyper- and hypotension. Let us look for relationships which hold under these diverse circumstances. Out of this maze of data comes the fact that the relationship which holds most closely is that described by Starling. The work of the normal heart is related to its size. Data obtained in a wide diversity of clinical conditions agree with results obtained in experiments with the isolated heart and lungs of the dog. We have a right to believe, therefore, in the wide applicability of this conception.

Figure 2 illustrates this relationship.¹⁹ The dots, representing the values obtained on persons without cardiac disease, arrange themselves along the line AB, and are bounded by the lines CD and EF. The circles represent the values obtained on persons who were once decompensated, so we know that they have myocardial disease. They obviously occupy a different place on the chart. Not only can one conclude that under normal conditions the work of the heart per beat is a function of its size but one also can say that, in hearts known to be abnormal, this law does not hold.¹⁹ Here, then, is a method which has the promise of identifying hearts with abnormal myocardia.

But it must be realized that this method has its limitations. Cases of coronary disease cannot be detected by the relationship of heart work to heart size. Perhaps the amount of heart muscle affected is ordinarily too small a proportion of the total to be detected in resting patients. But this line of thought gives promise of permitting the detection of the myocardial dysfunction characteristic of that great group of cases whose end is congestive failure.

Perhaps you now expect us to give you instructions how to find the heart's work and size on your patients. We cannot do so. Cardiac output estimations are laborious and technically difficult. The recent improvements in our method have greatly increased the speed but have increased the complexity of apparatus. We see no means of simplifying our technique. So we cannot present to you the logical conclusion of our research, a simple practical method for the estimation of myocardial function. Indeed we do not believe that our primary aim should be to attain such a method. It should be to shed so much light on the problems of myocardial function that the signs and symptoms available to every physician will take on new meaning, and thus permit more accurate estimations of the condi-

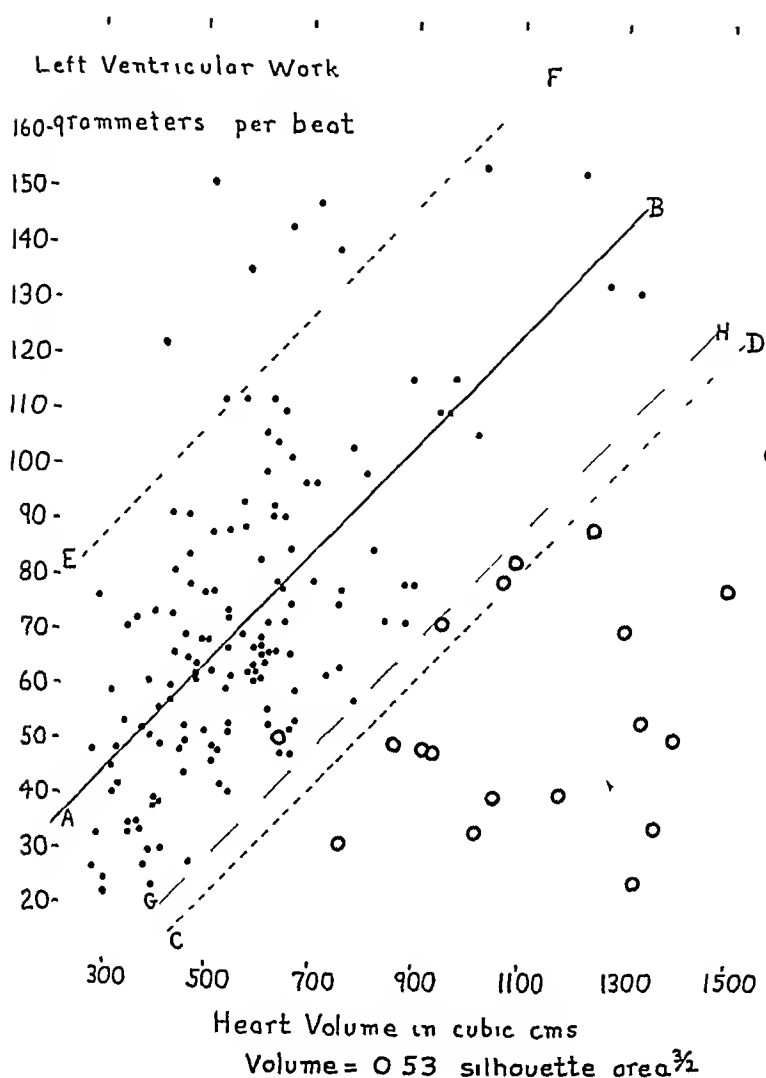


FIG 2 Evidence that the "Law of the Heart" holds for clinical conditions, and can be used to detect cases with abnormal myocardial function. Each symbol represents the average of duplicate estimations of basal cardiac work. The *dots* indicate the values obtained on normal persons and patients without evidence of cardiac disease. The *circles* indicate values obtained on persons who formerly had cardiac decompensation, they had regained compensation by the time the estimations were made. The dots arrange themselves about the line AB whose position has been calculated from the data. The positions of CD and EF were likewise obtained by statistical methods, their distance from AB is twice the standard deviation of the data. Therefore if any result falls to the right of CD the probability of its being abnormal is about 97.5 in 100. GH is the line, parallel with AB, which most cleanly divides the dots from the circles and so it may be thought of as the lower limit of the normal zone. (Reprinted by permission of the *Journal of Clinical Investigation*)

tion of the heart with resulting improvement in the prevention and treatment of its diseases

When our data are searched with this in mind many things are found which throw light on clinical problems. One may be emphasized here. A moderate increase in size of the heart may be physiological. In the few

conditions in which heart work is ordinarily increased, hyperthyroidism, hypertension and anemia, a moderate increase in heart size is not necessarily an indication of myocardial dysfunction. But, in general, in all other conditions, increased cardiac size is the best objective sign of myocardial weakness and it deserves all the emphasis that clinicians have long put upon it.

BIBLIOGRAPHY

The results cited may be found in the publications given below or in papers referred to therein.

- 1 BOCK, H E. Das Minutenvolumen des Herzens im Liegen und Stehen, *Ztschr f d Ges Exper Med*, 1934, *xcii*, 782-792.
- 2 CHRISTENSEN, H E. Om Hjaertets Minu volumen, *Bibliotek f Laeger*, 1933, *Lviii* and *Munksgaard*, Copenhagen.
- 3 Cournand, A, BRYAN, N A, and RICHARDS, D W, JR. Cardiac output in relation to unilateral pneumothorax in man, *Jr Clin Invest*, 1935, *xiv*, 181-189.
- 4 DONAL, J S, JR, GAMBLE, C J, and SHAW, R. Cardiac output in man, adaptation of katharometer for rapid determination of ethyl iodide in estimations of cardiac output by ethyl iodide method, *Am Jr Physiol*, 1934, *ci*, 666.
- 5 EWIG, W, and HINSBERG, K. Kreislaufstudien, neue Methode zur Bestimmung des Herzminutenvolumens *Ztschr f klin Med*, 1930, *cxx*, 693-731.
- 6 GROLLMAN, A. Cardiac output of man in health and disease, 1932, Charles C Thomas, Springfield.
- 7 GROLLMAN, A, and FERRIGAN, J P, JR. Cardiac output, its related functions in case of coarctation of aorta, *Arch Int Med*, 1934, *lxi*, 35-38.
- 8 LAPLACE, L B. Observations on the effect of an arteriovenous fistula on the human circulation, *Am Jr Med Sci*, 1935, *clxxxix*, 497-506.
- 9 LEWIS, T. Studies of capillary pulsation, *Heart*, 1924, *xi*, 151-193.
- 10 LISHOLM, E, NYLIN, G, and QUARNA, K. *Acta Radiologica*, 1934, *xv*, 237.
- 11 MALTBY, A B. Cardiac output in Pick syndrome, *Proc Soc Exper Biol and Med*, 1934, *xxx*, 853-854.
- 12 NORLIN, G. Das Minutenvolumen des Herzens bei experimenteller Azidose, *Skand Arch f Physiol*, 1933, *lxvii*, 170-176.
- 13 NORLIN, G, and SKOGLUND, C R. Über den Einfluss einiger in der Therapie gebrauchten elektrischen Stromformen auf das Minutenvolumen des Herzens, *Skand Arch f Physiol*, 1933, *lxvii*, 36-46.
- 14 NYLIN, G. Clinical tests of function of heart, *Acta med Scandinav*, 1933, *lii*, 1-92.
- 15 NYLIN, G. Relation between heart volume and stroke volume in recumbent and erect positions, *Skand Arch f Physiol*, 1934, *lxix*, 237-246.
- 16 STARLING, E H. The principles of human physiology, 4th ed, 1926, Lea and Febiger, Philadelphia.
- 17 STARR, I, JR, and COLLINS, L H, JR. Studies of cardiac output in normal men, *Am Jr Physiol*, 1931, *xcvi*, 228-242.
- 18 STARR, I, JR, COLLINS, L H, JR, and WOOD, F C. Studies of basal work and output of heart in clinical conditions, *Jr Clin Invest*, 1933, *xii*, 13-43.
- 19 STARR, I, JR, and others. Studies of heart and circulation in disease, *Jr Clin Invest*, 1934, *xiii*, 561-592.
- 20 STARR, I, JR, DONAL, J S, MARGOLIES, A, and GAMBLE, C J. (To be published.)
- 21 SYLLABA, J. *Bull Internat d Acad d Sci de Bohême*, 1934, Prague.

STUDIES ON THE INCREASED METABOLISM IN HYPERTHYROIDISM

By E. COWLES ANDRUS, M D , F A C P , and DONALD McEACHERN, M D ,
Baltimore, Maryland

THE metabolic phenomena characteristic of hyperthyroidism are common to both the clinical and the experimental forms. In the clinical disease, these changes may only be observed en masse. They may be measured only as they are reflected in the *total* displacement of certain equilibria such as the oxygen consumption, carbon dioxide production, glucose tolerance, nitrogen balance, and the creatine metabolism.

Experimental hyperthyroidism may be produced in animals to any desired degree by the administration of thyroid extract or by the injection of thyroxine. Under these circumstances it is possible to analyze the metabolic alterations and to subject various elements thereof to quantitative chemical examination. By analogy, at least, the results of such observations are applicable to the clinical disease.

In the light of accumulated experience these metabolic effects have been more and more accurately described and defined. Their appearance is delayed by an interval (15 to 24 hours) corresponding to the latent period characteristic of the action of thyroxine. They are not dependent upon the integrity of the nervous system.¹ Experiments conducted in vitro suggest that the effect of thyroxine is restricted to intact cells, upon minced tissue it is ineffective.² Of particular significance is the fact that, once established in the intact animal, certain metabolic changes persist in representative tissues after isolation from the body.

For example, if an animal receives thyroid extract by mouth or thyroxine by injection there ensues a series of phenomena quite analogous to those observed in clinical hyperthyroidism: nervousness, weakness and fatigability, tachycardia, hyperglycemia, loss of weight and increase in the basal metabolic rate. If the heart is removed from such an animal and is artificially perfused, it continues to beat for hours at a rate conspicuously more rapid than those of the untreated control animals. This persistent tachycardia indicates that the action of thyroxine survives the isolation of the tissues or organs. It has been fully described and analyzed elsewhere.³ It suffices to point out here that this effect is uninfluenced by iodine or iodides.

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

From the Cardiographic Laboratory, Department of Medicine, Johns Hopkins University and Hospital.

† Under a Fellowship of the National Research Council, Washington, D. C., and a Jacques Loeb Fellowship and a Bingham Fellowship of the Johns Hopkins Hospital and University, Baltimore.

Observations upon the oxygen consumption of tissues isolated from an hyperthyroid animal have demonstrated considerable and constant increases, in comparison with tissues of normal controls. Typical curves are shown in figure 1. Samples of the cells of the kidney, liver and diaphragm of thyroxinized animals consume oxygen at rates conspicuously in excess of those of similar tissues from normal animals. Such effects have also been demon-

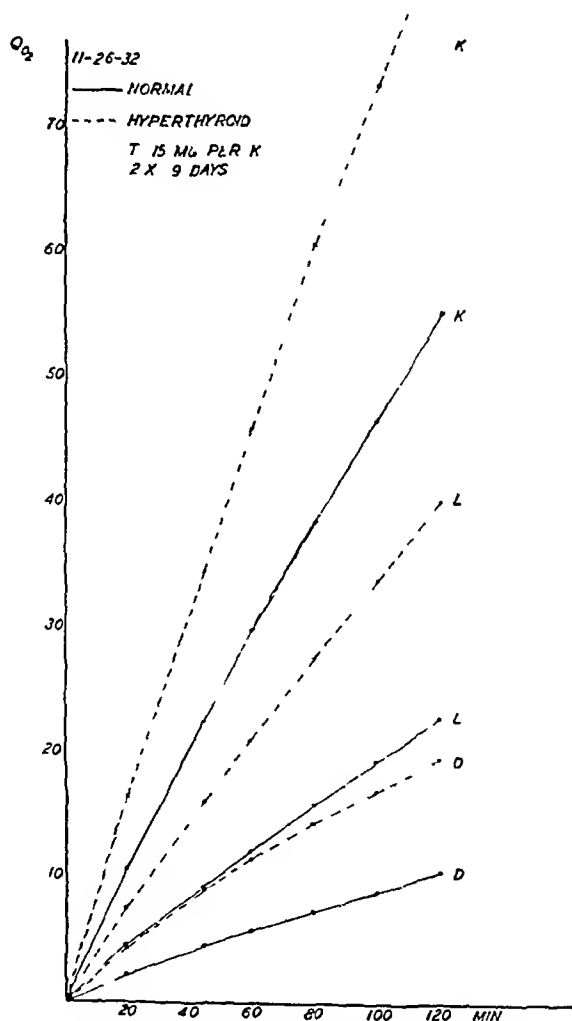


FIG 1 Typical curve of oxygen uptake by tissues from a normal and from an hyperthyroid animal

strated in other cells as diversified as those of the spleen, heart, nerve, and lung. Moreover, similar and commensurate increases of tissue respiration have been observed following the production of the hyperthyroid state by injection of anterior pituitary extract containing the thyrotropic hormone.⁴

Like the tachycardia of the surviving heart, the augmented oxygen utilization of the isolated tissue is uninfluenced by iodine. Studies have been

made in an effort to analyze this effect of thyroxine, to compare the increased increment of respiration with other phases of cellular metabolism and with the respiration of normal tissue

In the first place the authors have examined the theory that this increased oxygen consumption is secondary to the effect of thyroxine upon the metabolism of carbohydrate. Meakins⁵ has summarized the important aspects of the carbohydrate metabolism of muscle as related particularly to circulatory failure. There is abundant clinical and experimental evidence that in

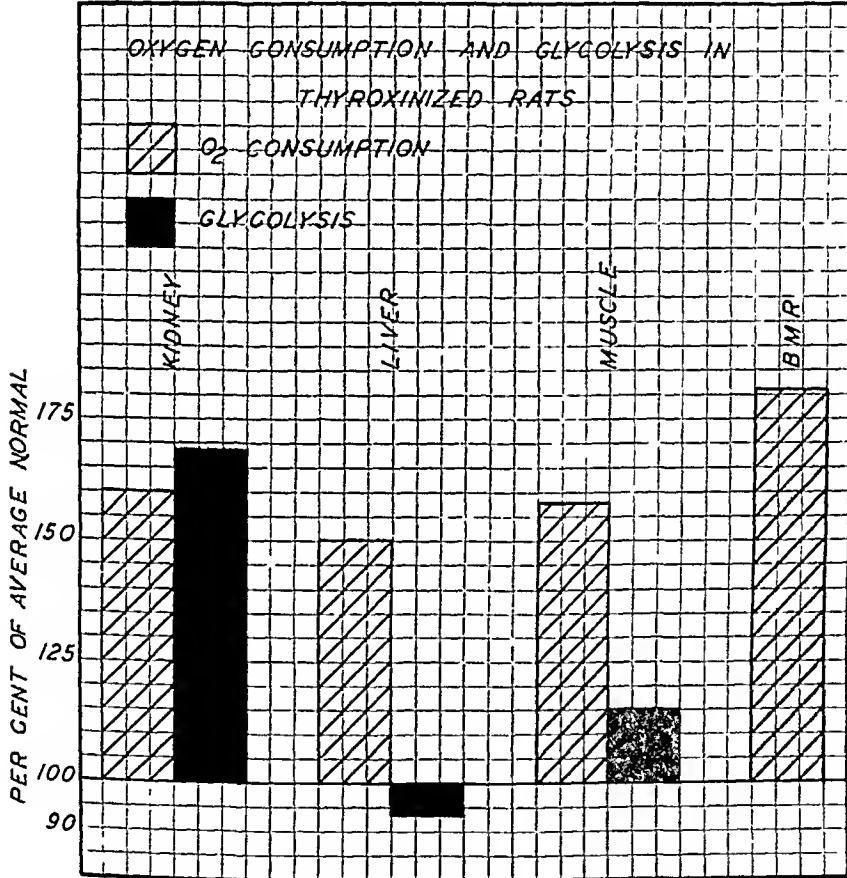


FIG 2 Comparing the basal metabolic rate with the oxygen consumption and glycolysis in surviving tissues of thyroxinized rats

hyperthyroidism this phase of metabolism may be profoundly affected the glycogen stores are depleted and, under conditions which normally lead to its production, lactic acid accumulates in the blood. The demand for oxygen to bring about the oxidative removal of excessive amounts of lactic acid has been supposed to explain the increased oxygen consumption characteristic of hyperthyroidism.⁶

Experiments calculated to test this theory have been reported elsewhere.^{7,8} In brief summary it has not been possible to protect animals

from the metabolic effects of thyroxine by the administration of substances—sodium fluoride and moniodoacetic acid—which interfere, at various stages, with the breakdown of carbohydrate to lactic acid. Furthermore, while the augmented oxygen utilization persists in the tissues of the hyperthyroid animal after isolation from the body, a commensurate increase of carbohydrate breakdown can be demonstrated only in the case of kidney tissue (Figure 2). It is therefore to be concluded that the increased

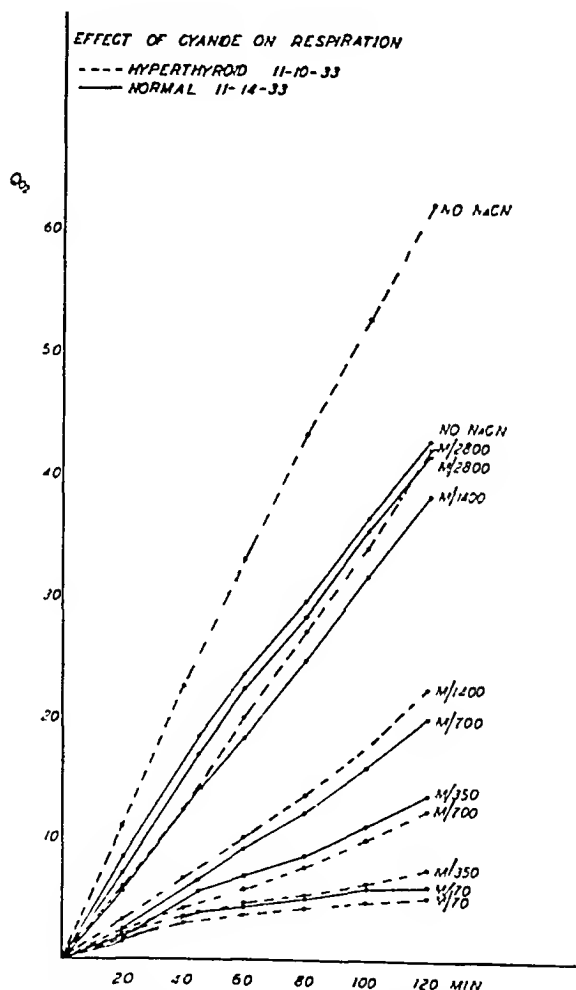


FIG 3 Oxygen consumption of kidney tissue from normal and thyroxinized rats in various concentrations of sodium cyanide

oxygen consumption in hyperthyroidism is not primarily due to an augmented carbohydrate metabolism.

The extra increment of respiration in the tissues of the thyroxinized animal has been compared to the respiration of normal tissues in its reaction to the influence of cyanide. The normal tissue respiration may be almost completely inhibited by this substance^{9,10}. It has been demonstrated that the increased oxygen consumption induced by thyroxine is likewise sensitive

to cyanide. Indeed it may be inhibited by cyanide in concentrations which produce little or no effect upon the oxygen consumption of normal tissues. The results are summarized in figure 3 which depicts the oxygen utilization of kidney tissue from normal and thyroxinized rats in various concentrations of sodium cyanide. In M/2800 solution the curves nearly coincide.

Finally, it has been possible to show that the effects of thyroxine persist, not only in the isolated tissue of an animal to which it has been administered but in an aqueous enzyme-containing extract thereof. Normal muscle tissue contains a powerful enzyme soluble in water and capable of

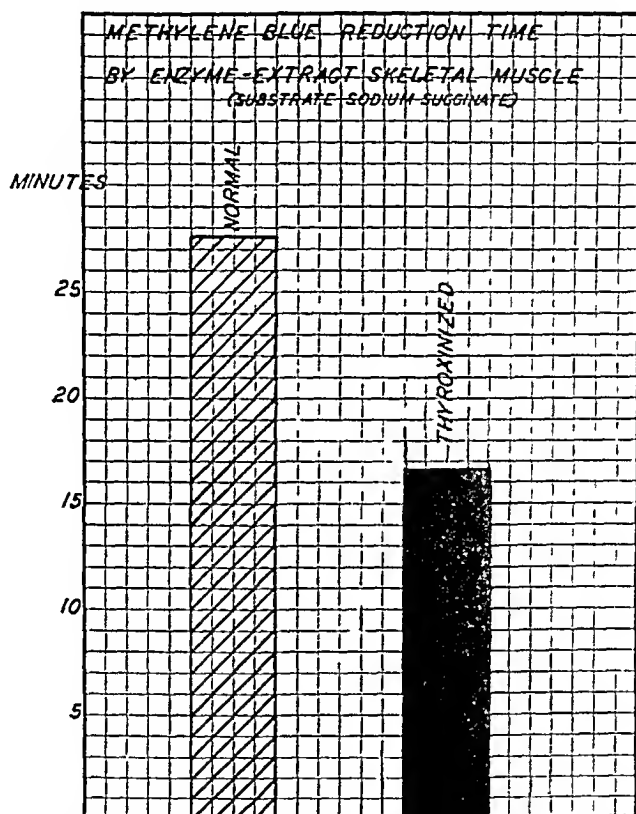


FIG 4 Indicating increased enzymatic activity in the aqueous extract of muscle from thyroxinized rabbits

dehydrogenating succinic acid to fumaric acid in the presence of a suitable hydrogen acceptor. Methylene blue may act as such an acceptor, becoming decolorized in the process, and the rate of its decolorization serves as a measure of the speed of the reaction. Aqueous extracts have been prepared from muscle tissue of normal and of thyroxinized animals and have been compared by means of this reaction. The average time required for decolorization of the dye by the enzyme extracts from normal animals' tissues was greater by 60 per cent than those from the thyroxinized animals (figure

* This does not imply that cyanide may be used with benefit to inhibit the primary metabolic action of thyroxine. Its effect is upon a mechanism vital to the cell.¹¹

4) It appears that, as regards this example of tissue enzyme, under the influence of thyroxine it is increased in amount or potency

In certain fundamental respects, then, the action of thyroxine upon tissue metabolism survives the isolation of the cells from the remainder of the organism, or even in substances extractable from such cells. Conversely, the effects of thyroid insufficiency also become inherent in the tissue cells, and are manifest *in vitro* in the *decreased* activity of certain enzymes¹². It is to be assumed that the thyroid secretion is indispensable among the factors which preside over the normal metabolism of the tissues. Abnormality may result in case of excess or deficiency.

These observations may be offered in explanation of certain features of clinical hyperthyroidism (thyrotoxicosis). This syndrome combines the manifestations of an excess of thyroid secretion with the events which lead to that excess. The production of exophthalmos, so long regarded as distinguishing clinical hyperthyroidism (Graves' disease) from the experimental form, has recently been accomplished by Marine¹³. It is, apparently, an accompaniment of events which, in addition, lead to the augmented secretion of the thyroid substance.

It is to be concluded that the effects of thyroxine upon the patient with hyperthyroidism include the metabolic phenomena demonstrable in the isolated tissue in the experimental disease. These effects are undoubtedly widespread and involve, perhaps to varying degree, the cells of all the metabolizing tissues in the body. The primary result is an increase in the metabolic requirements of each tissue. These are collectively manifest in the increased utilization of oxygen by the patient at rest, and in loss of weight unless the daily caloric intake is considerably raised. It is probable, too, that the excessively rapid heart beat is, in part, an expression of the effect of thyroxine upon the metabolism of the cardiac muscle.

Moreover, there may ensue, perhaps secondarily, an impairment of the integrity of tissues or organs. Functional insufficiency may result in any tissue whenever the physiological demands upon it approach or exceed the limits set by its own metabolism. The occurrence of congestive heart failure and of angina pectoris in hyperthyroidism clearly exemplifies such imbalance. The relief of angina pectoris by thyroidectomy, in the presence or absence of hyperthyroidism,¹⁴ is no doubt due as much to the resultant lowered metabolic requirements of the heart muscle as to the decrease in the circulatory load. The relief by thyroidectomy of arteriosclerotic gangrene in an elderly patient with hyperthyroidism, observed * on the Medical Service of the Johns Hopkins Hospital, is almost certainly due to the consequent reduction in the demands of the tissue to meet the available blood supply.

These observations contribute nothing directly to the therapy of hyperthyroidism. It is to be emphasized that none of the metabolic phenomena which survive in the isolated tissue are abated by iodine. In this sense the

* To be reported

results confirm the opinion, recently reaffirmed by Means and Lerman,¹⁵ that the beneficial effect of iodine in hyperthyroidism is exerted upon the gland itself with consequent diminution of its secretion. For the present the treatment of the metabolic phenomena must be directed toward the reduction of the amount of circulating thyroxine.

SUMMARY

The metabolic effects of thyroxine, produced in animals, survive in the tissues after isolation from the body and in substances extractable from such tissues. Analysis of these effects indicates (1) that the metabolism of many varieties of cells is augmented, (2) that the activity of certain tissue enzymes is increased in the process, and (3) that these effects are not inhibited by iodine. By analogy it is suggested that the metabolic phenomena of clinical hyperthyroidism include those demonstrated in the experimental type. It is emphasized that the beneficial effect of iodine upon the clinical disease is primarily upon the thyroid gland and only secondarily upon the metabolic phenomena resulting from the excessive thyroid secretion.

BIBLIOGRAPHY

- 1 RIML, O. and WOLFF, H. G. Zur Frage des Angriffspunktes der stoffwechselsteigernden Schilddrüsenwirkung, *Arch f exper Path u Pharmacol*, 1930, clvii, 178-192
- 2 DAVIS, J. E., DACOSTA, E., and HASTINGS, A. B. Effect of thyroxine on the tissue metabolism of the excised frog heart, *Am Jr Physiol*, 1934, cx, 187-190
- 3 LEWIS, J. K., and MCEACHERN, D. Persistence of an accelerated rate in the isolated hearts of thyrotoxic rabbits: response to iodides, thyroxine and epinephrine, *Bull Johns Hopkins Hosp*, 1931, xlviii, 228-241
- 4 REISS, M., HOCKWALD, A., and DRUCKREY, H. Thyreotroper Wirkstoff des Hypophysenvorderlappens und Gewebsstoffwechsel, *Med Klin*, 1933, xxx, 1112-1113
- 5 MEAKINS, J. C. Modern muscle physiology and circulatory failure, *ANN INT MED*, 1932, vi, 506-513
- 6 HAFFNER, F. Pharmakologische Untersuchungen mit einem deutschen Thyroxin, *Klin Wchnschr*, 1927, vi, 1932-1935
- 7 ANDRUS, E. C., and MCEACHERN, D. An investigation of the lactic acid metabolism in hyperthyroidism, *Trans Assoc Am Phys*, 1934, xlii, 65-75
- 8 MCEACHERN, D. The metabolism of isolated surviving tissues from animals rendered hyperthyroid with thyroxine, *Bull Johns Hopkins Hosp*, 1935, lvi, 145
- 9 ALT, H. L. Über die Atmungshemmung durch Blausäure, *Biochem Ztschr*, 1930, ccxli, 498-501
- 10 WARBURG, O. Über Nicht-Hemmung der Zellatmung durch Blausäure, *Biochem Ztschr*, 1931, ccxxii, 493-497
- 11 REID, A. Das sauerstoffübertragende Ferment der Atmung, *Fortschr d Med*, 1932, l, 133-134
- 12 DYE, J. A., and WAGGENER, R. A. Studies in tissue respiration and endocrine function. I. The influence of thyroidectomy on the iodophenol oxidase content of animal tissues, *Am Jr Physiol*, 1928, lxxv, 1-13
- 13 MARINE, D., and ROSEN, S. H. The exophthalmos of Graves' disease. Its experimental production and significance, *Am Jr Med Sci*, 1934, clxxxviii, 565-571
- 14 BLUMGART, H. L., LEVINE, S. A., and BERLIN, D. D. Congestive heart failure and angina pectoris. The therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity, *Arch Int Med*, 1933, li, 866-877
- 15 MEANS, J. H. and LERMAN, J. The action of thyroxine in thyrotoxicosis, *Jr Am Med Assoc*, 1935, civ, 969-972

STUDIES RELATING VITAMIN C DEFICIENCY TO RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS, EXPERIMENTAL, CLINICAL, AND GENERAL CONSIDERATIONS

I RHEUMATIC FEVER

By JAMES F RINEHART, M D , *San Francisco, California*

ON the basis of experimental data previously reported^{1,2} the concept was presented that rheumatic fever may be the result of the combined influence of vitamin C deficiency and infection. It is the purpose of this communication briefly to review this and to summarize further confirmatory experimental observations and other data accumulated during the past three years that would appear to support this thesis.

Experimental Method The methods employed are essentially similar to those reported^{1,2}. Guinea pigs were maintained on a basic diet adequate in all food factors except vitamin C. Regulating the intake of vitamin C by giving small measured amounts of orange juice, the animals were maintained for varying periods of time in acute and subacute or chronic states of vitamin C deficiency or scurvy. In the original observations the infecting agents used were various strains of a beta hemolytic streptococcus, which cause spontaneous lymphadenitis in guinea pigs. In the subsequent work other organisms have been used including a gamma type streptococcus and *B. bronchosepticus*, also derived from spontaneous guinea pig infections. The experimental work has included a study of the pathological effects of acute, subacute and chronic scurvy alone, of similar degrees of scurvy combined with infection and, as controls, infected and non-infected animals maintained on the same basic diet adequately supplemented with orange juice. Inasmuch as pathological findings are in essential agreement with those previously reported, they may be briefly summarized and illustrated.

With respect to the rôle of infection, it may briefly be said that in the presence of adequate vitamin C nutrition, rheumatic type lesions have not been observed. When superimposed on vitamin C deficiency, essentially similar observations have been made with the several infecting agents used. It would appear, however, irrespective of the precise organism used, that a high degree of virulence favors the development of significant pathological changes. Further, in the conduct of the experiments it has become quite apparent that the defense mechanism of the vitamin C deficient animals is less effective, and that the ability to localize the infecting organism is impaired.

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935.

This work has been made possible by research funds granted from the Christine Breon Fund for Medical Research.

The second and final part of Dr. Rinehart's article will be published in the December number of the ANNALS.

LESIONS IN THE HEART VALVES

In uncomplicated vitamin C deficiency, definite atrophic and degenerative changes occur in the collagenous stroma of the heart valves. In scurvy with superimposed infection, striking lesions of a combined degenerative and proliferative character develop in the heart valves with considerable frequency. These lesions present many basic similarities to the early lesions of rheumatic fever. Poynton and Schlesinger³ have pointed out that the valvular vegetations owe their formation to subendothelial proliferation of cells and not to a primary destruction of the endothelium. Ribbert⁴ speaks of characteristic changes in the subendocardial tissues beneath the thrombus or beneath the free surfaces, consisting in an enlargement of and gradual increase in the number of cells whose cytoplasm enlarges and consequently causes a mild thickening of the tissues. This change, he finds, is accompanied by a transformation of the "*zwischen-substanz*" which becomes clearer, more translucent, and the fibrillar structure less distinct. Clawson⁵ too has noted the essentially proliferative character of the inflammatory process in rheumatic fever. The accompanying illustrations will serve to

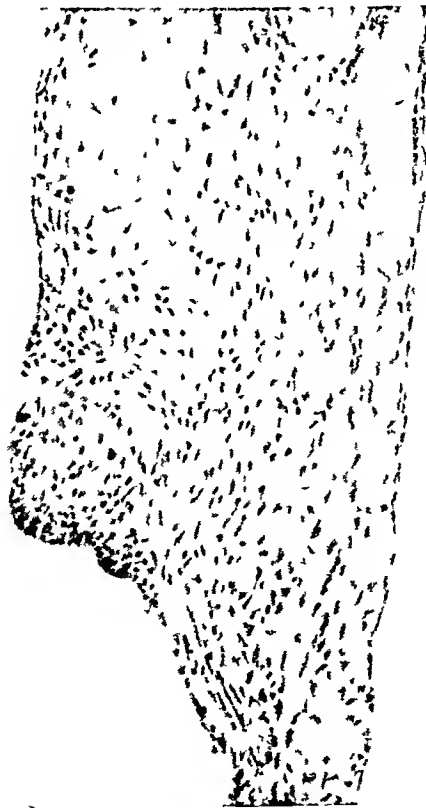


FIG 1 Mitral valve, scurvy plus infection (gamma streptococcus). Showing diffuse swelling of the valve substance, impoverishment of collagenous stroma and an early proliferation of the stroma cells, just beneath the contact surface. $\times 90$

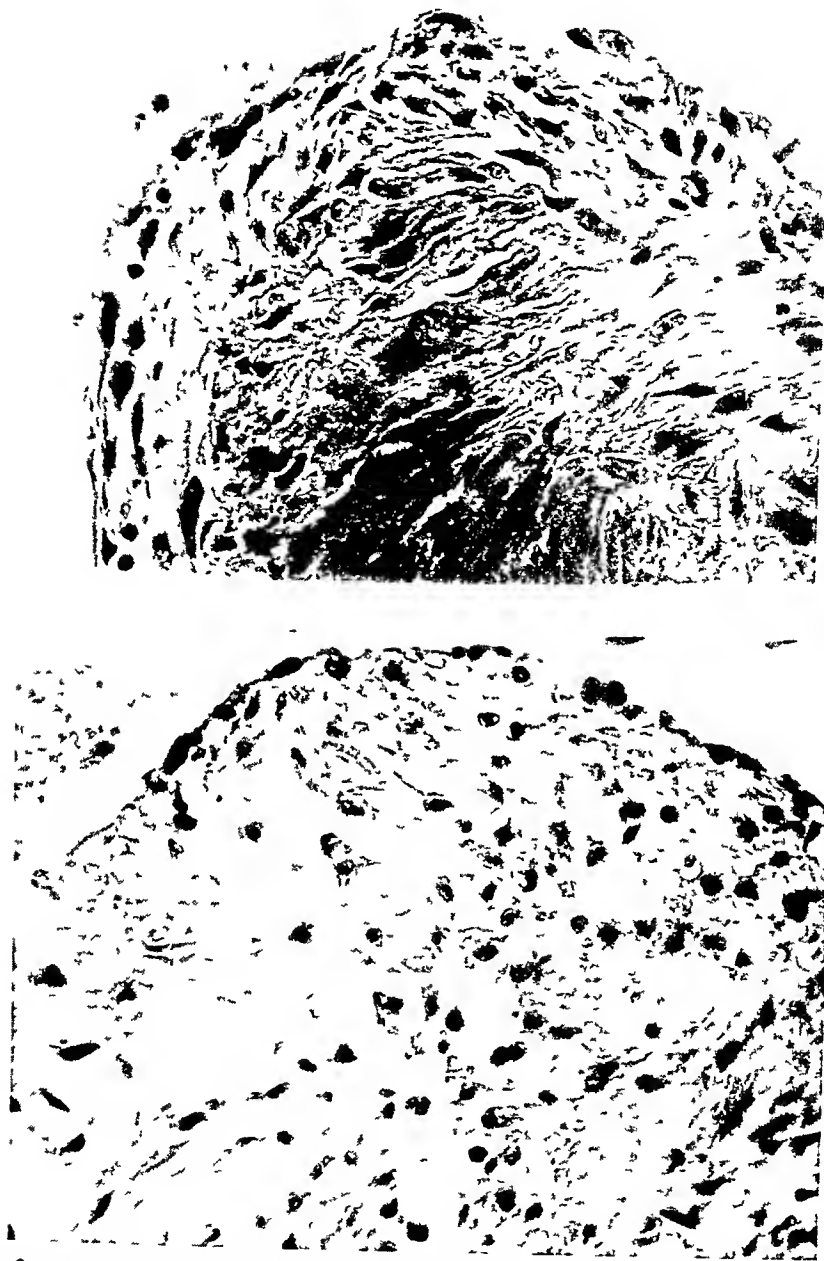
show the character of the experimental lesions and their basic similarity to those of rheumatic fever

Figure 1 shows a moderate diffuse interstitial proliferative reaction in the mitral valve in an animal subjected to scurvy and an experimentally induced lymphadenitis due to a gamma type streptococcus. This lesion is an example of the milder type and corresponds closely to Ribbert's description of the early rheumatic valvulitis. In figure 2 is shown an intense prolifera-



FIG 2 Aortic valve, subacute or chronic scurvy plus infection (beta streptococcus). A striking proliferative reaction in two leaflets of the aortic valve. The normal regular collagenous stroma is gone. Large hyperplastic cells actively proliferate in an edematous stroma. Fragments of an unidentified hyaline material are present in the substance of the valve. The endothelial lining of the contact surfaces is interrupted and a thin film of fibrin merges with the underlying valve substance. $\times 120$

tive lesion in the aortic valve that occurred in an early experimental series in which an acute local infection due to a beta type streptococcus was superimposed upon the scorbutic state. The rather intense proliferative reaction in two leaflets of the aortic valve is shown. Fragments of an unidentified hyaline substance resembling swollen collagen are present in the substance of the valve. The endothelial lining of the contact surface is interrupted and a thin film of brilliant fibrin merges with the valve substance in this



FIGS 3 and 4 Figure 3 (above) shows a typical early rheumatic verrucous endocarditis. Figure 4 (below), an experimental lesion in an animal subjected to acute scurvy with superimposed infection (beta streptococcus). The striking similarity of the two lesions is apparent. In each instance, a peculiar hyaline substance and an associated cellular proliferation constitute the verrucous nodule. Approximately $\times 450$.

region. The proliferating cells showing hyperchromatic nuclei and an abundant dully eosinophilic cytoplasm correspond closely to the reactive cells of rheumatic fever. The remarkably close resemblance that the experimental endocarditis may bear to that of rheumatic fever is shown in figures

3 and 4 Figure 3 is a characteristic verrucous lesion of rheumatic fever.⁴ This and the experimental lesion (figure 4) show a hyalinized material within the valve substance which with the associated cellular proliferation constitute the verrucous nodule. The experimental lesion was produced in this instance by the combined influence of a relatively acute scurvy and infection with a beta streptococcus.

The pathological changes encountered in the heart muscle are less strik-

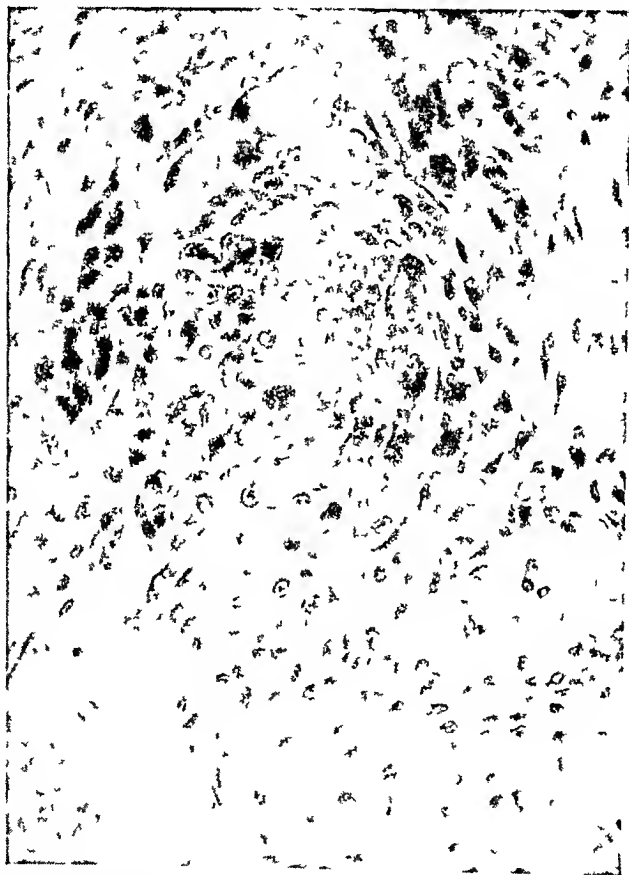


FIG 5 A concentric large cell proliferative reaction in the endocardium adjoining the heart muscle near the angle of attachment of the mitral valve. Relatively acute scurvy plus infection (subcutaneous) with *B. aertrycke*. Similar lesions have been seen with other infecting agents when combined with vitamin C deficiency. The general character of the lesion as well as the individual cytoplasmic and nuclear characters of the cells recall the Aschoff reaction of rheumatic fever. $\times 400$

ing than the valvulitis described. However, proliferative reactions are not infrequently seen in the heart muscle, beneath the endocardium and in the pericardium which are considered fundamentally similar to the Aschoff reaction. Figure 5 shows a local proliferative reaction which was found at the angle of attachment near the base of the mitral valve. The con-

* This photograph, used to illustrate a typical rheumatic endocarditis by Dr. Clawson,⁵ was kindly furnished by him and is published with his permission.

centric lesion is composed of large hyperchromatic connective tissue cells. The general arrangement and cellular constituents are much like those in the Aschoff body. Figure 6 shows one of a number of nodular proliferative reactions that have been seen in the pericardium of experimental animals. In a few instances the "fibrinoid" degeneration of Klinge⁶ has been noted in the heart muscle. However, experimentally this change is much more frequently seen in the articular tissue.

It would appear that the more delicate connective tissue supportive struc-



FIG. 6 A localized proliferative reaction in the pericardium. Subacute scurvy plus infection (gamma streptococcus) $\times 500$

ture of the guinea pig heart might account for the less striking interstitial reactions.

PATHOLOGY OF THE JOINTS

An early manifestation of vitamin C deficiency in the guinea pig is an arthropathy characterized by pain, tenderness, and swelling of the joints. The detail of the relationship of vitamin C deficiency to joint pathology is best reserved for the subsequent section dealing with arthritis. However, it may be said that the essential changes encountered in and about the joints² in subacute scurvy with or without infection correspond closely to those

described by Klinge and Grzimek⁷ in careful pathological studies of the lesions in the arthritis of rheumatic fever. The occasional occurrence in the experimental animals of subcutaneous nodules is of great interest. This finding, too, will be discussed in the consideration of the scorbutic arthropathy.

GENERAL CONSIDERATIONS

The Problem of Hemorrhage It is usual to think of scurvy as a disease characterized by the occurrence of widespread hemorrhage. It is true that hemorrhage is commonly encountered in vitamin C deficiency due to impairment of the intercellular substance supporting capillaries. However, the degree of hemorrhage seen is dependent to a great extent upon time factors and the intensity of the deficiency. Hemorrhagic manifestations in rheumatic fever are of more frequent occurrence than it is generally considered. Poynton and Paine⁸ have described blood stained synovial fluid in rheumatic arthritis. Chester and Schwartz⁹ have noted the rather frequent occurrence of purpuric lesions on the skin of the legs and arms in rheumatic fever and consider this as a clinical evidence of recurrent activity of the disease. A recent study of Coburn¹⁰ would indicate that hemorrhage is characteristic of the acute phases of rheumatic fever, noting that "in all patients dying during marked activity of the rheumatic process, hemorrhagic lesions were widespread." In cases of sepsis, hemorrhages are of course common but as pointed out by Coburn¹⁰ the hemorrhages of rheumatic fever cannot be assigned to sepsis. A scorbutic factor in rheumatic fever would appear to offer a satisfactory explanation for the hemorrhagic manifestations of the disease.

Similarities of the Fundamental Pathology of Scurvy and Rheumatic Fever Certain fundamental considerations would strongly favor the concept that vitamin C deficiency may play a rôle in rheumatic fever. The histological studies of Aschoff and Koch,¹¹ Hojer,¹² Wolbach and Howe¹³ have demonstrated that the scorbutic animal is not able to form normal intercellular cement substances. Collagen is of course the most widely distributed intercellular substance in the body. Hojer¹² emphasized the occurrence of degenerated or imperfectly formed collagen even in early and relatively mild degrees of scurvy. It is apparent that the heart valves and peri-articular tissues are sites in which connective tissue substances are subjected to greatest stress. It would be here then that the first evidence of an inadequacy would become manifest. Klinge⁶ in careful studies of the histopathology of rheumatic fever emphasizes the importance of a peculiar alteration seen in connective tissues which he has called a "fibrinoid" degeneration. This he considers the initial and characteristic lesion of rheumatic fever. The exact interpretation of this change is not entirely clear. It is my opinion that in some instances it represents an imperfect collagen intimately associated with fibrin derived from blood plasma exuded from regional capillaries. Regardless of the exact nature of the "fibrinoid"

degeneration, a seemingly identical lesion is seen in the experimental animals, particularly in the tissues about the joints and less commonly in the heart muscle

DISCUSSION

It is believed that the experimental work reported offers strong evidence that vitamin C deficiency in conjunction with infection may operate as an important factor in the etiology of rheumatic fever. Experiments conducted over a period of years have given essentially consistent findings. Supportive experimental data have been published by Stimson, Hedley and Rose¹¹. The possibilities of the experimental approach, however, have in no way been exhausted. Among other things the minimal degree of vitamin C deficiency which with infection will produce significant lesions, has not been determined. Further, the pathology corresponding to that of a *chronic* rheumatic endocarditis has not been produced. The mode of operation of the factor of infection has not been determined. In the majority of instances we have seen no evidence of bacterial localization in the proliferative endocardial lesions. However, in one instance large numbers of bacteria were seen directly associated with such a lesion. We do not know whether the infection acts through the mechanism of a toxin or through localization of small numbers of organisms which evade detection. It is considered very significant, however, that a variety of infecting organisms in adequately nourished animals have in no way produced comparable "rheumatic type" lesions.

EPIDEMIOLOGICAL CONSIDERATIONS

An analysis of the known epidemiology of rheumatic fever would appear to strengthen the concept reported. In fact, careful scrutiny of clinical and epidemiological data has not only afforded nothing contradictory but rather has given confirmatory evidence. It would appear that the known predisposing factors in rheumatic fever, which are considered below, could be explained on the basis of vitamin C deficiency.

Malnutrition and Rheumatic Fever. Numerous observers have called attention to the frequent association of malnutrition with rheumatic fever. Vining¹⁵ emphasized the malnourished state of the pre-rheumatic child and suggested the existence of vitamin B deficiency. Campbell and Warner¹⁶ agree that it is the debilitated child that develops rheumatic fever. Swift¹⁷ observes that most rheumatic children appear undernourished. McLean¹⁸ found 82 per cent of rheumatic children underweight for their height. Certain symptoms which include fatigue, loss of appetite, loss of weight, muscle pains, and nervousness are common to both latent scurvy and to the pre-rheumatic or early rheumatic state. A mild anemia is another finding common to the two conditions.

Geographic Distribution. Rheumatic fever is a disease of the temperate zone. Clarke¹⁹ has drawn attention to its practical absence in the tropics. The natural dietaries in the various sections of the tropics are well supplied

with anti-scorbutics and scurvy is rarely encountered in the tropics except under unusual circumstances as those that sometimes prevail in labor camps or military campaigns. The observations of Sir Leonard Rogers²⁰ are of particular interest. Speaking of India, he states "heart diseases were half as common as in London and rheumatic endocarditis was quite absent although streptococcal infections were otherwise as frequent." The comparative rarity of rheumatic fever and rheumatoid arthritis in Holland has been pointed out by van Breeman²¹. The importance of truck gardening and the dairy industry in Holland suggests that the dietary might be more than usually adequate in vitamin C-containing foods.

Social Incidence The social incidence particularly suggests an environmental factor in the etiology of rheumatic fever. Campbell and Warner¹⁶ find rheumatic disease the most crippling affection of the poor. Swift²² notes that statistics show obvious rheumatic fever is 15 to 20 times more frequent in the laboring classes than in those forming the bulk of private practice. Glover²³ believes the true incidence of rheumatic fever in England to be directly proportional to the degree of poverty and estimates the occurrence of acute rheumatism is 20 or even 30 times as great in the poor as in the well-to-do. It would seem to the writer that a disease with such an amazingly dominant incidence in poorer people could not be explained on the basis of a specific bacterial infection or on the basis of recurrent non-specific respiratory infection alone. Some fundamental environmental factor would appear to lie in the background.

Age Incidence Acute rheumatic fever is in the main a disease of childhood. The maximum incidence of first attacks occurs between the ages of five and twelve. This is a period of active growth in which the nutritional requirements are great. It has recently been shown²⁴ that children of elementary school age require approximately twice as much vitamin C per kilo for the prevention of latent scurvy as is needed by adults.

Urban Incidence and Familial Tendency The higher incidence of rheumatic fever in cities would appear explainable on the basis of greater liability to respiratory infection and, for the poorer classes, less adequate nutrition. Similarly the basis of the high familial tendency might lie in a common unhealthy bacterial and nutritional environment.

Seasonal Incidence Suggestive evidence of a possible relation of latent scurvy and rheumatic fever is present in the concurrent seasonal incidence of the two diseases. All authors are agreed that the greatest incidence of rheumatic fever in this country is in the late winter and early spring. This is a season following a period of diminished availability of fresh fruits and vegetables in which scurvy either latent or manifest would be expected to occur.

THE RÔLE OF INFECTION IN RHEUMATIC FEVER

A consideration of the rôle of infection in rheumatic fever has been summarized in a previous publication.² A factor of infection would appear to

be thoroughly established. A specific infecting agent has not been established. Streptococci of various types have been implicated. Recent studies^{25, 26} have pointed to a beta hemolytic streptococcus as the common offender. However, infection alone does not appear to afford an adequate explanation of the disease. Coburn²⁵ has stressed the occurrence of a wave of upper respiratory infections preceding the development of a lesser wave of rheumatic fever. Only a small minority of those suffering the infection develop rheumatic fever. It would appear that some mechanism renders this smaller group susceptible to the disease. It is the author's concept that this mechanism is a state of latent or sub-manifest scurvy. The writer wishes to make it entirely clear that the factor of infection in rheumatic fever is in no sense minimized. Clinical data as well as the experimental studies indicate the importance of infection in this disease. Beta hemolytic streptococci, perhaps because they are the most common cause of acute upper respiratory infections, are probably the most important associated organisms. Further, the experimental work does not preclude the possible influence of allergic factors. Indeed the work of Sulzberger and Oser²⁷ indicates that moderate vitamin C deficiency favors the development of hypersensitivity to neoarsphenamine. A latent scurvy might likewise favor the development of bacterial hypersensitivity.

THE EXISTENCE OF LATENT SCURVY

The recognition of latent deficiency states has offered a problem of considerable difficulty. Until recently the approach to the problem of latent scurvy has been largely through indirect evidence. A method of definite but limited value for the detection of vitamin C deficiency is afforded by the determination of the capillary strength. Using this method as a criterion, Gothlin²⁸ found evidence of vitamin C undernutrition in about 18 per cent of the school children (between 11 and 14 years) in the province of Uppland (Sweden) during the months of April and May. Dalldorf²⁹ similarly using capillary resistance tests, considers that a mild degree of vitamin C deficiency may constitute a problem of considerable public health importance. A recent survey of food purchases of families on relief³⁰ in a California city revealed some striking and unexpected data. It was found that purchases of vitamin C-containing foods in a high percentage of cases fell far below the standard considered necessary for adequate nutrition. To quote from the study: "If the choice of food in a California market, in the middle of summer when the variety of fresh fruits and vegetables is at a maximum and the cost at a minimum, shows this deficiency, what is to be expected of other localities during the winter months is appalling."

The recent chemical identification of vitamin C has stimulated extensive researches that promise rapid progress in our knowledge. Yavorsky, Almaden and King,³¹ in titration of extracts of tissues obtained post mortem, found that "latent human scurvy, generally unobserved in clinical practice,

is fairly common." Of 31 cases under 10 years of age, four were in a range so low that latent scurvy was clearly evident. Of 36 cases over 10 years of age, six showed critically low vitamin C content of tissues indicating a depletion nearly as severe as found in terminal human or guinea pig scurvy. The evidence derived from clinical, nutritional, and chemical studies then all points toward the existence of latent scurvy.

STORAGE, UTILIZATION AND DEPLETION OF VITAMIN C

The ability of the body to store vitamin C is limited. The rapid elimination of large quantities of vitamin C after ingestion, and the continued loss from the body without a dietary source being supplied, has been shown by Harris, Ray, and Ward³². Practically nothing is known with respect to factors which may hinder or prevent absorption or utilization of vitamin C. There is a certain amount of indirect evidence that achlorhydria may increase the basic requirement³³. Factors which may deplete stores of vitamin C are of great interest and probably of great importance. Our own experience from experimental observation is that certain infections may act in this way. Dry³⁴ states that scurvy may be precipitated by infective febrile illnesses. Harde and Benjamin³⁵ have presented brief evidence that infection may deplete the organic stores of vitamin C. Van Eekelen and Kooy³⁶ have shown that fatigue may operate in a similar fashion. Studies of factors conditioning absorption and causing organic depletion of vitamin C are of great importance and should be extended. If acute infection depletes the organic store of vitamin C, it is of great importance to the concept presented in this paper. Under such circumstances a mild grade of deficiency might by infection be rendered significantly severe in a relatively short period of time. It would appear that such a mechanism might explain the latent phase noted by many observers between the acute respiratory infection and clinical onset of rheumatic fever.

CLINICAL STUDIES

During the past 18 months a clinical approach to the problem has been made in association with Dr. Amos Christie in the Childrens' Cardiac Clinic of the University of California Medical School³⁷. Although the duration of the study is not considered long enough to be conclusive, many interesting data have been collected. The general method of study has included dietary histories, assay of social environment, and capillary resistance tests as well as routine clinical examination and periodic follow-up. Enquiry into the dietary habits indicates that the majority of the children lie on the borderline of inadequate nutrition. Many were severely deficient in vitamin C intake particularly during the winter months. In many instances the economic status precluded adequate food purchases, in other cases racial habits or individual idiosyncrasies led to a very low consumption of vitamin C-containing foods. Capillary resistance tests (an index of latent scurvy)

revealed in general low levels, particularly in cases with clinical evidence of recent rheumatic activity. Many cases showed edematous puffy gums. After an initial survey the patients were instructed to provide generous amounts of vitamin C in the diet. The usual recommendation was to prescribe a definite daily dietary supplement of orange juice (eight to sixteen ounces). Where the individuals were unable to provide this, efforts were made to secure aid from various social agencies. In most cases the period of follow-up has not been long enough to be conclusive. The group, however, has done surprisingly well from the standpoint of weight gain, general clinical improvement and absence of recurrence. The levels of capillary strength have risen. Many have passed through acute upper respiratory infections without reactivation of the rheumatic process. One recurrence occurred in a patient whom we knew had not been able to cooperate. When placed in a convalescent home where a very generous intake of vitamin C was given, the child responded remarkably with a gain of 21 pounds in eight weeks. We are cognizant of the difficulties of this method of study and particularly of the necessity of a long period of observation. Within this limit, however, we feel that the study has been very encouraging.

SUMMARY

The experimental basis for the concept that rheumatic fever may be the result of the combined action of vitamin C deficiency and infection is reviewed. Further experimental studies are reported which confirm the original observations that this deficiency with superimposed infection produces in the guinea pig a disease state with many pathologic similarities to rheumatic fever. Comparable lesions develop in the heart valves, heart muscle and joints. The occasional occurrence of subcutaneous nodules remarkably like those of rheumatic fever would appear to complete the pathologic similarity.

Evidence is presented that the factor of infection is not specific. Essentially similar lesions develop when different organisms are used as the infecting agents. The same infections do not cause rheumatic type lesions in animals receiving adequate amounts of vitamin C.

It is suggested that vitamin C deficiency may afford the basis for the hemorrhagic manifestations frequently observed in rheumatic fever.

The epidemiological peculiarities of rheumatic fever, notably its social, geographic, and seasonal incidence, might be explained on the operation of a scorbutic factor in the disease.

Evidence indicating not only the existence, but the probably frequent occurrence of latent scurvy is reviewed. The relatively high vitamin C requirements of children, the limited capacity to store the vitamin and the possible influence of infection or fatigue in depleting this organic reserve is discussed.

Clinical studies in progress are cited that have afforded encouraging data.

CONCLUSIONS

On the basis of further experimental studies and clinical and epidemiological data, the thesis is reaffirmed that rheumatic fever may result from the combined influence of vitamin C deficiency and infection

REFERENCES

- 1 RINEHART, J F, and MITTIFR, S R The heart valves and muscle in experimental scurvy with superimposed infection With notes on the similarity of the lesions to those of rheumatic fever, *Am Jr Path*, 1934, x, 61-79
- 2 RINEHART, J F, CONNOR, C L, and MITTIFR, S R Further observations on pathologic similarities between experimental scurvy combined with infection and rheumatic fever, *Jr Exper Med*, 1934, lx, 97-114
- 3 POYNTON, F J, and SCHLESINGER, B Recent advances in the study of rheumatism, 1931, P Blakiston's Son and Co, Inc, Philadelphia
- 4 RIBBERT, H Die Erkrankungen des Endokards Handbuch der speziellen pathologischen Anatomie und Histologie, by HENKE and LUBARSCH, Julius Springer, Berlin, 1924, II, 217
- 5 CLAWSON, B J An analysis of 220 cases of endocarditis, *Arch Int Med*, 1924, xxxiii, 157-184
- 6 KLINGE, F Das Gewebsbild des fieberhaften Rheumatismus XII Mitteilung Zusammenfassende kritische Betrachtung zur Frage der geweblichen Sonderstellung des rheumatischen Gewebsschadens, *Virehow's Arch f path Anat*, 1932, ccxxvii, 344-388
- 7 KLINGE, F, and GRZIMEK, N Das Gewebsbild des fieberhaften Rheumatismus VI Mitteilung Der chronische Gelenkrheumatismus (Infektarthritis, Polyarthritis lenta) und über "rheumatische Stigmata," *Virehow's Arch f path Anat*, 1932, ccxxvii, 646-712
- 8 POYNTON, F J, and PAINE, A Researches on rheumatism, 1914, Macmillan Co, New York
- 9 CHESTER, W, and SCHWARTZ, S P Cutaneous lesions in rheumatic fever, *Am Jr Dis Child*, 1934, xlviii, 69-80
- 10 COBURN, A F Relationship of the rheumatic process to the development of alterations in tissues, *Am Jr Dis Child*, 1933, xlv, 933-972
- 11 ASCHOFF, L, and KOCH, W Skorbut, eine pathologisch-anatomische Studie, 1919, Gustav Fischer, Jena
- 12 HOJER, J A Studies in scurvy, *Acta Paediat*, Suppl, Almquist and Wiksells, Upsala, 1924, III
- 13 WOLBACH, S B, and HOWE, P R Intercellular substances in experimental scorbutus, *Arch Path*, 1926, I, 1-24
- 14 STIMSON, A M, HEDLEY, O F, and ROSE, E Notes on experimental rheumatic fever, *Public Health Reports*, 1934, xlix, 361-363
- 15 VINING, C W The prerheumatic child, *Med Jr and Rec*, 1928, cxxviii, 351-354, 395-398, 453-455
- 16 CAMPBELL, M, and WARNER, E C A study of rheumatic disease in children, *Lancet*, 1930, I, 61-66
- 17 SWIFT, H F Rheumatic fever, *Nelson Loose-leaf Medicine*, Thomas Nelson and Sons, New York, 1931, I, 401-430
- 18 McLEAN, C C Early manifestations of rheumatic infections in young children, *ANN INT MED*, 1932, v 1357-1366
- 19 CLARKE, J T The geographical distribution of rheumatic fever, *Jr Trop Med and Hyg*, 1930, xxxiii, 249-258
- 20 ROGERS, L Discussion of life assurance in the tropics, *Brit Med Jr*, 1928, I, 219

- 21 VAN BREEMAN, J Types of rheumatic disorders most prevalent in Holland *Med Jr and Rec*, 1928, cxviii, 469-472
- 22 SWIFT, H F Factors favoring the onset and continuation of rheumatic fever, *Am Heart Jr*, 1931, vi, 625-637
- 23 GLOVER, A Discussion on the etiology of acute rheumatism and chorea in relation to social and environmental factors, *Proc Royal Soc Med*, 1934, xxvii, 953
- 24 FALK, G, GEDDA, K, and GOTHLIN, G F An investigation into the strength of the skin capillaries and indirectly into the vitamin C standard of school children in the district of Norbotten, north of the Arctic Circle, *Upsala Lakaref Forh*, 1932, xxxviii, 1-24
- 25 COBURN, A F The factor of infection in the rheumatic state, 1931, Williams and Wilkins, Baltimore
- 26 COLLIS, W R F The contagious factor in the etiology of rheumatic fever, *Am Jr Dis Child*, 1932, xlv, 485-493
- 27 SULZBERGER, M, and OSER, B L Influence of ascorbic acid of diet on sensitization of guinea pigs to neoarsphenamine, *Proc Soc Exper Biol and Med*, 1935, xxxii, 716-719
- 28 GOTHLIN, G B A method of establishing the vitamin C standard and requirements of physically healthy individuals by testing the strength of their cutaneous capillaries, *Skandin Arch f Physiol*, 1931, lx, 225-270
- 29 DALLDORF, G A sensitive test for subclinical scurvy, *Am Jr Dis Child*, 1933, xlv, 794-802
- 30 OKEY, R Nutritive value of foods purchased by dependent families Report of Hellar Committee for Research in Social Economics, 1934, University of California
- 31 YAVORSKY, M, ALMADEN, P, and KING, G C The vitamin C content of human tissues, *Jr Biol Chem*, 1934, cvi, 525-529
- 32 HARRIS, L J, RAY, S N, and WARD, A The excretion of vitamin C in human urine and its dependence on the dietary intake, *Biochem Jr*, 1933, xxvii, 2010-2015
- 33 SCHULTZER, P Studies on capillary resistance, *Acta med Scandinav*, 1934, xxxci, 113-132
- 34 DRY, T J Avitaminosis in the natives of Rhodesia, *Arch Int Med*, 1933, li, 679-691
- 35 HARDE, E, and BENJAMIN, H R Vitamin C content of tissues of laboratory animals under various pathological conditions, *Proc Soc Exper Biol and Med*, 1935, xxxii, 651-653
- 36 VAN EEKELEN, M, and KOOL, R The ascorbic acid content of the suprarenal glands and liver from normal and fatigued rats, *Acta Brevia Neerlandica*, 1933, iii, 169-171
- 37 CHRISTIE, A U, and RINEHART, J F Unpublished studies on the clinical significance of vitamin C deficiency in rheumatic fever

NON-TRAUMATIC CHYLOTHORAX AND CHYLOPERICARDIUM, REVIEW AND REPORT OF A CASE DUE TO CARCINOMATOUS THROMBOANGIITIS OBLITERANS OF THE THORACIC DUCT AND UPPER GREAT VEINS¹

By WALLACE M. YATER, M.D., F.A.C.P., *Washington, D. C.*

CHYLOTHORAX is a rare condition and chylopericardium still more so. Traumatic chylothorax due to rupture or section of the thoracic duct is apparently even more rare than the non-traumatic form, at least in so far as may be judged from the literature. Mouchet (1933) studied 43 cases of traumatic chylothorax reported in the literature. Perhaps twice this number of cases of the non-traumatic form have been reported.

MORBID ANATOMY

Although the exact cause of the chylothorax in many of the non-traumatic cases has not been determined, and though careful studies of the thoracic duct and veins in such cases are rare, yet review of the literature of this condition reveals that certain common causes have been demonstrated. The commonest cause seems to be compression or invasion and occlusion of the thoracic duct by a metastatic malignant tumor, sometimes with, but usually without thrombotic occlusion of the great veins of the upper part of the body. Bargebuhr (1894) reported a case due to carcinomatous invasion and occlusion of the thoracic duct secondary to carcinoma of the stomach and quoted the cases of Morison (1691), Hoffman (1700), Bass (1723), Chelchowski (1890), Zawadzki (1891), Reichenbach (2 cases, 1891), Leidhecker (1893) and two additional cases of his own, all associated with neoplasms of the abdomen or thorax. In some of the cases chylous ascites also existed. The chylothorax was thought to be due to occlusion of the thoracic duct by compression by a mass or to actual neoplastic infiltration and occlusion of the duct. Carcinoma was the lesion in some of the cases, malignant lymphoma in others. Rotmann (1896) recorded three other cases from the literature due to carcinomatous involvement of the thoracic duct. Shaw (1899) reported a case of Hodgkin's disease in which the thoracic duct, which was double, became two cordlike structures buried in glands. Dock's case, studied at necropsy by Warthin (1907), was one of lymphosarcoma in which the thoracic duct had been converted into a solid cord by neoplastic invasion. In the cases of Fellner (1907) and Furth (1927) the duct was buried in a mediastinal lymphosarcomatous mass. The cases of Saigente, Decastello and Ruddell were ap-

¹ Submitted for publication July 1, 1935.

From the Georgetown University School of Medicine and the Department of Medicine of the Gallinger Municipal Hospital, Washington, D. C.

parently similar cases of Hodgkin's disease. Other cases due to carcinomatous occlusion, as ascertained by necropsy, were those of Virchow, Schiømm, Weigert, Cooper, Senator, Enzmann, Leschtschinski, Löffler, Hendricks, Gandin, Lyter and Fehr. The case of the last author (1930) was particularly well studied. There was carcinoma of the stomach with widespread metastases. Chylothorax was moderate but chylous ascites great. The inferior vena cava was thrombosed. The thoracic duct was buried in dense carcinomatous tissue. The coats of its wall were essentially intact, however, except for minute cancer nests in small lymph spaces in the adventitia, but its lumen was completely closed in the greater part of its course by dense connective tissue.

Perhaps the second most common cause of non-traumatic chylothorax is tuberculosis, but the mechanism here is not so obvious in some cases. Cases of this probable origin have been reported by Milton, Strauss, Bachmann, Boyer, Whitla, Morton, Hoppe-Seyler, Fowler and Godlee, Gullbring and Brandt. The case of the last named author (1917) was one with bilateral chylothorax and some chylous ascites. There was widespread miliary tuberculosis. Sections of the thoracic duct showed fibrous obliteration of the cervical portion, below which the lumen of the enlarged thoracic portion was filled with caseous masses and granulation tissue. In the wall of the duct were epithelioid cells and Langhans giant cells.

There remains a group of cases with miscellaneous causes of the chylothorax. In Rotmann's case 17 (1896) there was lymphangiectasis extending up through the abdominal lymphatics to those of the thorax. In Omerod-Wilk's case (1868) the left subclavian vein and its branches were occluded, there was also ascites. The cases of Opolzer, Renvers and Martin were quite similar in that some of the upper great veins were occluded by thrombi. Quincke (1875) reported a case in which there was inflammatory thickening of the mesentery with closure of the lymphatic vessels, resulting in both chylothorax and chylous ascites. Gandin's first case (1913) was a case of polyserositis, and his second case was one of cirrhosis of the liver, in both of which there was more chylous ascites than chylothorax. Oberndorfer (1925) reported a case of atherosclerosis of the duct, in which the lower two-thirds of the duct was filled with a blood thrombus, there was also cirrhosis of the liver and both chylothorax and chylous ascites. Engstad (1926) thought the chylothorax in his case of a large aneurysm of the aorta was due to specific ulceration of the thoracic duct. A necropsy was performed on the five-day old infant of Hilgenberg's (1929), but no cause for the chylothorax could be found. In Fehr's second case (1930), in which there was aortic regurgitation, the thoracic duct was surrounded by connective tissue, the lumen was closed and the wall was thickened with dense connective tissue. Steiner (1932) reported a case of pulmonary fibrosis in which the pleurae were 1 to 2 cm thick, but the thoracic duct was apparently normal. In Heppner's case of bilateral chylothorax and chylous

ascites the cause was probably traumatic rupture of the thoracic duct 2.5 cm above the diaphragm, although the reason for the rupture was not apparent.

Although this list of cases would seem to indicate that such occlusions of the thoracic duct necessarily lead to chylothorax, with or without chylous ascites, such is not the case. In the first place, there may be chylous ascites without chylothorax, and in the second place there may be neither. The former is demonstrated by the case of Monaldi (1933), in which there was gastric carcinoma with much secondary involvement of the thoracic duct but only chylous ascites. The latter is demonstrated by the cases of Andral, Rust and Otto, quoted by Boegehold (1883), of Creyx and Gauvenet (1912) and of Benda (1926), in all of which there was undoubted occlusion of the thoracic duct by malignant tissue but no accumulation of chylous fluid. Winkler and Schwedenberg, in a study of 24 reported cases of carcinomatous closure of the thoracic duct, found chylous ascites in only three. Also, 12 cases have been reported of non-tuberculous suppurative inflammation of the thoracic duct (Pappenheimer, Kiyloff, Minassiantz), with occlusion thereof by a purulent exudate, but without the accumulation of chylous fluid in any of the serous cavities. In the cases of Otto and of Ameuille and Perreau the thoracic duct was extensively involved by a tuberculous process similar to that in the case of Brandt, and yet there was no transudation of chyle. McFarland (1893) reported a case of chronic congestive heart failure with almost complete occlusion of the mouth of the thoracic duct by an inflammatory thrombus and thrombosis of the subclavian and jugular veins with beginning organization, there was no chylothorax. Bigger (1907) described a chylous cyst and Wuim (1927) a fibroma of the receptaculum chyli, neither of which caused chylous ascites.

Lammers believes that no new collaterals are formed when the thoracic duct is obstructed but that the chyle and lymph may go through normal collaterals to the veins, especially when there is not much stasis but only a change in the wall of the duct. Pressure in the duct is normally low, but when it is greatly increased lymphangiectasis may develop in the tributary lymphatics and small lymph vessels may rupture or lymph and chyle may transude. This condition is especially apt to occur when there is thrombosis of the great veins into which the lymph flows as well as occlusion of the thoracic duct itself.

Fehr has advanced the theory that gradual closure of the duct does not lead to the accumulation of chylous fluid unless the collaterals are also occluded. It is the latter he believes responsible for rupture or oozing from many small lymph vessels. That this theory is probably true was shown in 1922 by Lee in his experiments with cats, in which he used an intra-thoracic method for complete ligation of the thoracic duct, the only method so far developed that is apparently faultless. He showed that the integrity of the duct is not essential to the life of the animal and that accumulation of chylous fluid in the serous cavities rarely if ever results from occlusion of the duct alone. In some of his cases in which the ligation was absolute,

collateral lymph circulation was established to the right thoracic duct, while in other cases lymphaticovenous connections were found to exist between the thoracic duct and the azygos vein

Stuart summarizes well the variations in the communication between tributaries of the thoracic duct and the venous system, indicating how normal collaterals may carry the chyle and lymph to the veins when the duct is obstructed "The typical description of the thoracic duct as a single channel throughout its course may almost be regarded as a description of an abnormality, so frequently is it found to branch and subdivide. In its thoracic portion it is very common to find it breaking up into two divisions, which reunite higher, enclosing a space technically named an 'insula,' which is often crossed by a plexus of communicating channels. Rarely the duct may remain double throughout. These insulae in the thorax are surgically unimportant, but the same tendency may manifest itself at the termination of the duct in the neck, so that it either opens in a delta-like manner by several fine channels in its usual situation, or actually terminates in two or more important branches, which enter different veins. Teichmann regards this multiple insertion as normal. Not uncommonly one branch enters the left subclavian vein, while another joins the left internal jugular, sometimes they enter the right and the left subclavian respectively. Verneuil records a sixfold division, two branches ending in the left subclavian, two in the external jugular and two in the vertebral. Verneuil quotes the results of Boullard's researches, namely, that in 24 cases the opening of the duct was 18 times single, thrice double, twice triple, and once sixfold. Wendel, in 17 cases, once found the opening triple, thrice double, while in four instances there were several branches

"A second abnormality in the relation of the thoracic duct to the great veins is that it may, while terminating in a single channel, open in some more or less unusual situation. Thus it may enter the left subclavian vein, the left internal jugular, the right internal jugular, or the right subclavian, in the last case the right lymphatic duct generally ends in the veins of the left side of the neck. Wutzer reports a case of its termination in the vena azygos major at the sixth dorsal vertebra, and Henle, who had doubts with respect to several similar recorded instances, regards Wutzer's case as undeniable

"A third and extremely important point is the frequent existence of communications between the thoracic duct and the various veins during the upward course of the former through the abdomen and thorax. This we might expect from a study of comparative anatomy, for in birds lymphatics of the lower extremities open into the veins of the thigh and pelvis, in amphibians and fish analogous lymphatics have a corresponding ending, and in the pig there are said to be regular communications between the thoracic duct and the azygos vein. In man Wendel regards a branch between the duct and the azygos major as almost a normal condition. Connections with the iliac and lumbar veins, the inferior vena cava, and the left renal vein

through the lumbar lymphatics have also been observed. In some of the older cases it is possible that there had been pressure on the duct above, and that these connecting vessels had originally possessed only a tiny lumen. A good account of the variations in the thoracic duct in this and other respects is contained in the volume by Poirier, Cuneo, and Delamere."

SYMPTOMATOLOGY

Besides the cases already mentioned, in many of which necropsies were performed, a number of other cases of chylothorax have been described from the clinical standpoint only (Neuenkirchen, Whyte, Syers, Veiel sen, Campbell, Lotheissen, Erb, Kannenski, Rosin, Strasser, Sherman, Jennings and Rich, Lammers, Hyde, Sale, Gunder, de Lange, Chevrel, Lewin, Pisek, Hussey, Williamson, Gralka, Wilhelm, Remé, Stewart and Linner, Felts, Foley)*. In some of these clinical cases there was evidence of the probable underlying morbid anatomy causing the chylothorax. These were mainly cases of tuberculosis, Hodgkin's disease and lymphosarcoma. The ages of the patients varied from early infancy to moderately advanced old age. Males predominated. The symptoms and signs were naturally dependent upon the underlying cause and the amount of chylous accumulation. The first symptoms were sometimes those of massive pleural effusions. The amount of accumulated milky fluid was sometimes small, sometimes great. Occasionally both pleural cavities contained chylous fluid. Chylous ascites occurred in perhaps half of the cases and chylopericardium in three (including that here reported). The thorax was aspirated a variable number of times. In Felts' case the thorax was tapped 40 times and the abdomen 13 over a period of months, a total of 235 pounds of fluid being obtained with a loss in body weight of only eight pounds. Hyde tapped his patient 21 times, withdrawing 48,139 cc of chylous fluid. Milton withdrew 15 pints of chyle (23 pounds) from the pleural cavity at one sitting over a period of six hours, the patient recovering without further aspiration. Lammers' patient coughed up about one-quarter of a liter of chylous fluid on two occasions, and Campbell's patient 25 cc. Lyter's patient vomited milky fluid. Pisek gave his infant patient Sudan III and found the aspirated chylous fluid to have become pink. Stewart and Linner injected Congo red intraperitoneally and obtained pink chylous fluid from the chest.

Emaciation may result from loss of chyle, containing the fat absorbed from the lacteals. The degree of emaciation depends upon the appetite of the patient, the underlying morbid anatomy, the amount of chyle aspirated, the rapidity of its re-accumulation and the ratio between the amount of chyle entering the veins through collaterals and the amount transuding into the serous cavities. The degree of emaciation may be greater with traumatic rupture of the thoracic duct as long as the defect remains open because of the greater amount of chyle escaping directly into the serous cavities.

*A very few other cases of chylothorax have been reported in the literature, but they were either not available or could not be translated.

Felts' case, mentioned above, illustrates, however, the possibility of the benignity of the loss of chyle in large amounts under favorable conditions

In a few cases in which chylous fluid has been aspirated from serous cavities during life it has been found later at necropsy to have disappeared. This disappearance may have been due to the opening up of normal collaterals.

CHARACTER OF THE FLUID

There has been considerable discussion in the literature regarding the characteristics of the chylous fluid. The differentiation between chylous and chyloform or pseudo-chylous fluid has frequently been made, with what appears to be a lack of clear distinction. Chyloform fluid has been thought to be due to fatty degeneration of the leukocytes of a purulent exudate and if it exists is apparently even more rare than the abnormal accumulation of chyle itself. Even a third form of fluid has been described as lactescent, non-chylous fluid, a milky effusion in which there were no fat globules but a "glyco-proteid" (Lion). The probability is that chylous and chyloform fluids are essentially the same and are both due to transudation of chyle and lymph. There appears to be considerable difference in the chemical and physical properties of the fluid in different cases, and this may account for the distinction. The size of the fat droplets, the presence and amount of various lipids, especially lecithoprotein, the varying amounts of chyle, lymph and inflammatory and neoplastic exudates, and the character and quantity of food ingested are all factors. There is no parallelism between the degree of turbidity, milkiness or opalescence and the amount of fat. In general, the smaller the size of the fat droplets, the more lactescent the fluid.

Most knowledge of the composition of chyle has been obtained from the study of a mixture of chyle and lymph obtained through a cannula in the thoracic duct of dogs. The chyle of a mixed diet is a white opaque fluid, occasionally tinged red or yellow from an admixture with red blood cells. In herbivora it may be greenish from the presence of chlorophyll. It is alkaline due to the presence of carbonates and phosphates of sodium. The specific gravity ranges between 1.018 and 1.025. It has a salty taste. It possesses an odor due to volatile fatty acids. It coagulates on standing, and a top creamy layer forms. Shaking with ether after alkali is added causes the fluid to become clear. Microscopically, many fine fat granules are seen which have a peculiar Brownian movement. There may be some white blood cells, mainly lymphocytes.

The chemical analyses in man (Munk) of chyle and lymph are as follows:

	Chyle	Lymph
Water	92.2 per cent	95.2 per cent
Solid	7.8 " "	4.8 " "
Fibrin	0.1 " "	1.0 " "
Proteids	3.2 " "	3.5 " "
Fats, lecithin and cholesterol	3.3 " "	traces
Extractives	0.4 " "	0.4 " "
Salt	0.8 " "	0.8 " "

Exceptionally chyle contains more sugar than lymph. Chyle contains more fat than lymph and less protein than blood plasma. The amount of urea is greater than in blood. The soaps in chyle are less than 0.2 per cent, the fat being almost all neutral fat. The fat granules are less than one micron in diameter. For discussions on the characteristics of chylous and so-called chyloform fluids one may refer to the papers of Shaw, Sherman, Lammers, Gandin, Lewin and Furth.

The normal amount of chyle flowing through the duct (Noel Patton) is 130 to 195 c.c. per hour, being greater after a meal.

PROGNOSIS

The prognosis depends largely upon the underlying cause of the chylothorax. In many cases this is a fatal neoplastic disease. A number of recoveries have been reported, however, after one or more aspirations of the fluid. The condition may last for months or years, with or without recovery. Traumatic chylothorax is more favorable, since a small opening in the wall of the thoracic duct may become closed by a thrombus or the duct itself may become thrombosed. Also, if the duct is ligated below the defect the collaterals may carry the chyle and lymph to the veins.

TREATMENT

The treatment is mainly that of the underlying disease. The chyle should be aspirated if it causes much respiratory embarrassment, otherwise, it probably should not be withdrawn, since it is apt to re-accumulate rapidly. The diet probably should consist largely of carbohydrates and proteins, and fluid should be taken only between meals in small amounts at a time.

CASE REPORT

A white woman, aged 47 years, was admitted to the Gallinger Municipal Hospital on January 19, 1934, complaining of difficulty in breathing and swelling of the face and neck. She had been well prior to five weeks before admission, except for scarlet fever in childhood and pneumonia about 20 years before. She had two children. The family history was irrelevant. Five weeks before admission she had been handled roughly by her nephew who playfully attempted to demonstrate a wrestling bout he had just witnessed. Her neck had been bent painfully. The following day she first noticed swelling of the neck and face, which varied in amount from time to time. Four days before admission she began to have difficulty in breathing and noticed distention of the veins over the chest and in the neck.

On admission the patient appeared to be in extremis. She was very cyanotic and extremely dyspneic. Artificial respiration caused great diminution in the degree of cyanosis and made her comfortable. She spent the first night in a Drinker respirator. On examination the following day she was described as being a moderately obese woman, sitting upright and breathing rapidly and shallowly. The upper half of the body was definitely cyanotic. The face was slightly swollen, and the neck was so swollen that all landmarks were obliterated. There was edema of the chest wall down to the costal margin and distention of the superficial veins. From the fourth rib downward posteriorly and the third rib downward anteriorly on the

right side there were diminished tactile fremitus and dullness. The breath sounds in this region were distant with a bronchial quality. There were numerous inspiratory and expiratory rales. The spoken and whispered voice sounds were transmitted very distinctly. The physical signs on the left side were normal but exaggerated, with musical rales at the end of inspiration. The outline of the heart was not definite. The rate was 100 per minute with regular rhythm. The blood pressure in the right arm was 115 systolic but the diastolic could not be estimated, it was 140 systolic and 110 diastolic in the left arm. The abdomen was negative. A pelvic examination was not made because of the patient's serious condition. There was moderate edema of the upper extremities, none of the lower. The temperature was 100° F. The respiratory rate was 30 per minute. Aspiration of the right pleural space produced 1500 cc of a lactescent fluid, which on microscopic examination revealed myriads of fine globules possessing a Brownian movement. The chemical composition of this fluid was as follows:

Fat	2.04	per cent
Serum globulin	0.71	" "
Serum albumin	2.07	" "
Non-protein nitrogen	32	mg per 100 cc
Urea nitrogen	14	mg " " "
Chlorides	540	mg " " "
Cholesterol	80	mg " " "

Urinalysis was negative. The hemoglobin was 80 per cent, the erythrocytes numbered 4,870,000 and the white blood cells 8,600 per cubic millimeter of blood, with 52 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 24 per cent band cells, 3 per cent young cells, 14 per cent lymphocytes and 6 per cent large mononuclears. The blood urea nitrogen was 13 mg per 100 cc, the blood sugar 95 mg, the blood cholesterol 113 mg, the serum albumin 3.56 per cent and the serum globulin 0.97 per cent.

Fluoroscopic examinations of the chest showed varying amounts of fluid in both sides and an abnormal shadow in the anterior superior mediastinum.

The patient was in the hospital 10 days before death. Her chest was aspirated three more times, once on the left side (750 cc) and twice on the right side (1300 cc each). For a while she seemed to improve greatly, the dyspnea, edema and cyanosis all diminishing. After three days the temperature became normal and remained so. The pulse rate varied considerably from 68 to 128. There was apparently little loss of weight. Death occurred on January 30 during a sudden attack of severe orthopnea, in which there was very little cyanosis.

Necropsy Necropsy was performed under difficulties but quite thoroughly. The neck was markedly swollen, and there was pitting edema of the upper arms and of the thoracic wall. While cutting through the subcutaneous tissues and muscles of the chest wall, all of the veins were observed to be thrombosed. Upon opening the thoracic cavity a large amount of milk-like fluid poured out of both pleural cavities, there being approximately three liters in the right and two in the left. The pericardial sac was distended with about 250 cc of the same fluid, and the transverse diameter of the sac was about 13 cm. When the heart was removed the superior vena cava was seen to be filled with a crumbly, light gray thrombus, and its wall was thickened. As the vena cava was dissected upward, it was noted that both innominate veins were completely occluded by what appeared to be an organized thrombus. This condition existed up to a point above which the subclavian veins should have joined the jugular veins. The subclavian vein on each side was a mere fibrous cord and difficult to find. The jugular veins were filled with ordinary, non-organized thrombi, that on the left being distended to a diameter of 2 cm for a distance of about 4 cm, that on the right having about half this diameter. Some lymph nodes about 1.5 cm

long were noted near the superior vena cava, and on sectioning were found to be firm and white, resembling carcinomatous lymph nodes. The lymphatic vessels in the thorax were not grossly visible. The thoracic duct was dissected out from the cisterna chyli to its point of entrance into the jugular vein. It was apparently normal except for the final centimeter, where it was dilated to almost 3 mm and felt firm. A lymph node about 1 cm long was found near the mouth of the thoracic duct and appeared grossly carcinomatous. A right lymphatic duct could not be found. The inferior vena cava and the veins draining into it were not thrombosed. Grossly the heart was in every way normal. The lower lobes of the lungs were moderately collapsed, the upper lobes containing air and the left upper lobe being somewhat emphysematous. There were a few small adhesions at the apices and bases. The abdominal cavity did not contain fluid. The liver was moderately enlarged, extending downward about 5 cm below the right costal margin and about 10 cm below the xiphoid process. There were a few filmy fibrous adhesions over the upper surface of the liver. Similar adhesions joined the under surface of the right lobe of the liver and the great omentum. There were also a few adhesions over the posterior surface of the spleen, which was grossly normal. The abdominal viscera appeared normal, except the ovaries, which were carcinomatous. The right measured about 11 by 9 cm and consisted of a capsule tensely distended with a clear watery fluid which coagulated after it was placed in formalin. On the external surface there were papillomatous excrescences. The left ovary resembled it but measured only 5 by 3 cm. There was no evidence of gross metastases except to the lymph nodes previously mentioned in the superior mediastinum.

Microscopic Study Sections through the superior vena cava showed that vessel to be filled with a thrombus. Organization was extending into this from the wall of the vein and had reached about one-fifth of the distance to the center of the thrombus. No tumor cells were seen in the wall of the vessel or in the thrombus. One lymph node adjacent to the vein appeared to be normal except for the usual amount of anthracosis. Another small lymph node nearby showed some small groups of tumor cells in its peripheral portion. In the connective tissue adjacent to the vena cava some of the small veins and an occasional arteriole were surrounded by small lymphocytes. The vein wall was greatly altered.

Sections through the middle portion of the right innominate vein showed that vessel to be completely occluded by an organizing thrombus, the organization having extended in toward the middle of the lumen about half way. The greatly altered wall of the vein contained numerous small lymphocytes. A few endothelial-lined spaces in the peripheral portion of the thrombus contained tumor cells. It was impossible to trace the vein wall completely because of fusion with the surrounding tissues by a marked fibroblastic reaction (figure 1).

Sections through the right innominate vein at its point of origin showed it to be completely occluded by a completely organized thrombus containing many endothelial-lined spaces, many containing blood, others containing only nests of tumor cells. About those containing tumor cells were numerous small lymphocytes. Some of the small vascular channels in the thrombus were thrombosed. At some distance outside of the vein there was a group of large, rounded spaces lined by and containing in their lumen tumor cells and a network of fibrin. About these spaces was dense fibrous connective tissue, and the small vascular channels therein were densely surrounded by small lymphocytes.

Sections through the middle portion of the left innominate vein showed essentially the same picture as those through the same portion of the right, but no tumor cells were seen. More of the small vascular channels in the organizing thrombus contained thrombi.

Sections made at short intervals through the first 15 cm of the left innominate vein just below the junction of the jugular and subclavian veins showed that there



FIG 1 Partial cross section of the right innominate vein and surrounding tissue, showing the organized thrombus within the vein, nests of neoplastic cells just within its wall and the fibroblastic reaction in the adjacent connective tissue above $\times 60$

was complete occlusion by a thrombus which was completely organized by the oldest-appearing connective tissue just at the origin of the vein. In the lower sections of this part of the vein the central portion in the thrombus had not become organized. There were more small lymphocytes in the organized thrombus of the left innominate vein than in the thrombus of the right innominate vein at the same point. There were, however, fewer spaces containing tumor cells. At this point there were also fewer nests or channels containing tumor cells in the connective tissue surrounding the vein. What was apparently the subclavian vein was seen to be completely organized into a fibrous cord.

Just above this point, i.e., in the lowest portion of the left jugular vein, the same picture was seen, with the central portion of the thrombus unorganized. There were a very few spaces in the wall of the vein, just within its muscular coat, lined with tumor cells.

Sections through the dilated portion of the left jugular vein showed this to contain an unorganized thrombus. The wall of the vein was greatly altered, with increased vascularity and a rim of dense lymphocytic infiltration. A small adjacent lymph node did not contain tumor cells.

Sections at short intervals through the bulbous terminal portion of the thoracic duct showed that vessel to be double at that point and presenting the picture seen in advanced cases of thromboangitis obliterans. There remained none of the thrombus which had undoubtedly originally existed in the lumina. This had become completely organized and canalized by irregular channels of various sizes and shapes lined by endothelium. In each duct there was an eccentric, slit-like channel which apparently represented the main new channel of the duct. The organized thrombus of one of the ducts was particularly well vascularized. At isolated and infrequent points in the region where the intima of the ducts probably once existed there were spaces containing tumor cells (figures 2 and 3). Sections through the upper, middle and lower thirds of the main duct below its bulbous terminal portion showed the lumen to be open and the wall relatively little affected.

The lymph node in the immediate vicinity of the end of the thoracic duct contained many nests of tumor cells. The adenomatous nature of the neoplasms was well demonstrated in many of these nests. Some of the nests were endothelial-lined structures containing masses of tumor cells, others were spaces lined by tumor cells and presenting an adenomatous formation. There were also isolated tumor cells in many of the pulp sinusoids, indicating retrograde involvement of the node through its duct. The tumor cells were moderately large epithelial cells with round nuclei of about the same size. Many of the cells were "signet-ring" cells, usually larger than the others and containing a large vacuole-like portion with the nucleus more or less flattened and crescentic at the periphery. There was relatively little cytoplasm. The cells were well differentiated and strongly resembled those of the ovarian tumors. Many psammomatous bodies were seen in the cell nests. These were rounded masses having a black peripheral zone with a refractive central portion. They presented the appearance of whorls. Sections made through the tissue adjacent to this lymph node in the supposed region of its duct showed a structure which may have been the duct. It contained no tumor cells in its lumen.

Sections through the walls of the ovaries showed typical adenocarcinoma of papillary structure. There was one layer of columnar epithelial cells with elongated nuclei. Most of the groundwork was a delicate reticulum of young fibrous connective tissue. In some of the fimbriae this reticulum was a homogeneous, hyaline-like material containing a large number of extravasated erythrocytes.

Sections of the other organs revealed nothing of importance.

Interpretation of Evidence. The most logical interpretation of the series of events in this case is as follows. A few of the columnar epithelial cells of the poly-

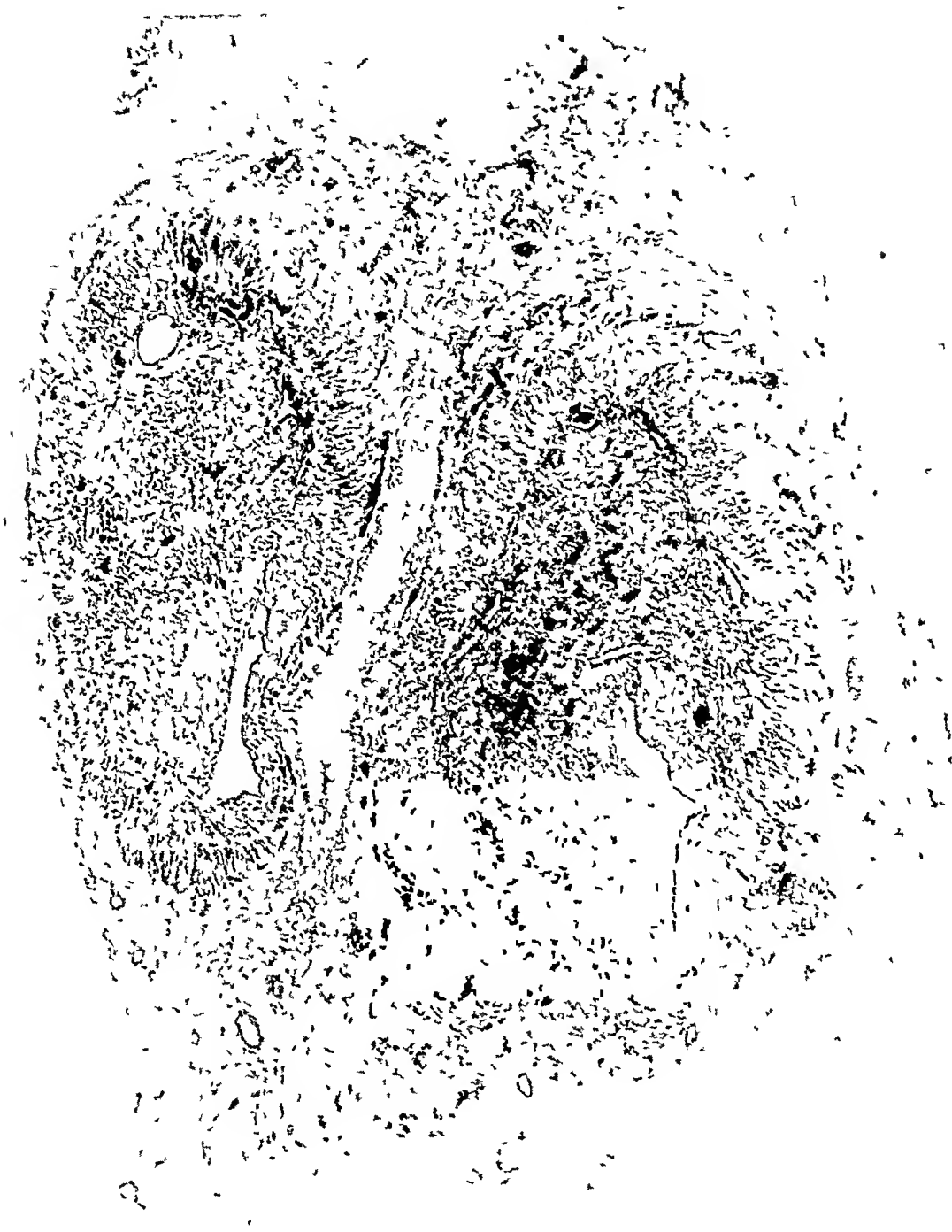


FIG 2 Cross section of the double terminal portion of the thoracic duct, showing the result of organization and canalization of thrombi in the lumina of the two arms. Small nests of carcinoma cells may be seen in the upper part of each vessel, in the probable region of the original intima. The organized thrombus of the vessel on the right is quite vascular. $\times 60$



FIG 3 Enlargement of the upper portion of the wall of the vessel on the left shown in figure 2. An endothelial-lined space containing carcinoma cells may be seen, to the left of which is a similar round space containing a psammoma-like body on its wall $\times 375$

moid carcinomata of the ovaries broke loose from the tumor or tumors into the peritoneal cavity. Here they were taken up by the lymphatics and entered the thoracic duct. They became lodged in the upper end of the duct, acted as an irritant to the intima and caused the formation of a thrombus which became organized and recanalized. Owing to the stasis in the duct produced by this obstruction some of the neoplastic cells were forced into the ducts of the lymph nodes in the superior mediastinum and began to proliferate in the nodes. Some of the cells lodged also in the walls of the upper great veins. There the same process was initiated on the intima of the veins as occurred in the thoracic duct. The injury to the neck probably speeded up the process of thrombosis and organization of these veins, causing damage to them in their indurated state.

SUMMARY AND CONCLUSIONS

1 Non-traumatic chylothorax is rare, perhaps less than 100 cases having been reported in the literature. Chylopericardium is very rare, only three cases, including the one here described, having been observed.

2 The commonest cause of non-traumatic chylothorax is apparently malignant neoplastic compression or occlusion of the thoracic duct, probably with closure of its collaterals. The second most common cause seems to be pulmonary, pleural, and glandular tuberculosis associated with occlusion of the thoracic duct and its collaterals. There is also a miscellaneous group of causes, chief among which is thrombotic occlusion of the great veins of the superior mediastinum.

3 Many cases of obstruction of the thoracic duct are not associated with the accumulation of chylous fluid because of the normal collaterals which empty into veins.

4 The physical and chemical composition of the chylous fluid probably depends largely upon the relative amounts therein of chyle, lymph, inflammatory and neoplastic exudates and lipids of varying chemical constitution and physical state. So-called chyliform fluid due to fatty degeneration of leukocytes in an inflammatory exudate probably does not exist.

5 Prognosis depends mainly upon the cause of the chylothorax, and treatment is largely symptomatic and supportive.

6 A case of bilateral chylothorax and chylopericardium is reported, with necropsy findings and detailed study of the thoracic duct and the upper great veins. The patient had bilateral cystadenocarcinoma of the ovaries with metastases to the upper end of the thoracic duct, the walls of the upper great veins and the lymph nodes of the superior mediastinum. The mouth of the thoracic duct and the veins had become thrombosed and organized. The duct had been recanalized.

BIBLIOGRAPHY

- AMEVILLE, P, and PERREAU, P. Thrombose tuberculeuse du canal thoracique, Bull et mem Soc med d hop de Paris, 1933, xlix, 1234-1237.
ANDRAL. Quoted by Boegehold.
BACHMANN. Quoted by Brandt.

- BARGELBUHR, A Chylose und Chyliforme Ergüsse in Pleura und Pericardialraum, *Deutsch Arch f klin Med*, 1894-95, liv, 410-441
- BASS Quoted by Bargebuhr
- BINDA, C Lymphogranulomatose des Ductus thoracicus, *Centralbl f allg Path u path Anat*, 1926, xxxvii, 544
- BIGGLR, H F A case of chylous cyst of the thoracic duct, *Cleveland Med Jr*, 1907, vi, 196-198
- BOEGRHOLD, E Über die Verletzungen des Ductus thoracicus, *Verhandl d deutsch Gesellsch f Chir*, 1883, p 122-147
- BOYR Quoted by Brandt
- BRANDT, M Ein Beitrag zur Kasuistik der Ductus thoracicus—Tuberkulose und des Chylothorax, *Inaug Diss Heidelberg, Universitäts-Buchdruckerei, Von J Horning*, 1917
- CAMPBELL, D G J A case of chylothorax, *Maritime Med News, Halifax*, 1906, viii, 295-297
- CHLICHOWSKI Quoted by Bargebuhr
- CHIHARI Quoted by Hussey
- COOPER Quoted by Furth
- CREY and GAUVINOT Cancer secondaire du canal thoracique, *Jr de med de Bordeaux*, 1912, xliii, 811-812
- DECASTELLO Quoted by Furth
- DE LANGE Quoted by Hussey
- DOCK, G Chylous ascites and chylous pleurisy, in a case of lymphocytoma involving the thoracic duct, *Trans Assoc Am Phys*, 1907, xxi, 464-476
- ENGSTAD, J E Chylothorax, *Lancet, Minn*, 1926, xli, 380
- ENZMANN Quoted by Furth
- ERB Quoted by Lotheissen
- FEHR, A Zur Kenntnis der Verödung des Ductus thoracicus, *Virchow's Arch f path Anat u Phys*, 1930-31, cclxxx, 265-272
- FELLNER, B Chylothorax bei Leukosarkom, *Mitt d Gesellsch f inn Med u Kinderh in Wien*, 1907, vi, 179
- FELTS, R L Chylothorax, with report of a case, *South Med and Surg*, 1927, lxxvii, 168-169
- FOLFY, G A case of chylous pleurisy, *Prensa Med Argent*, 1933, xx, 62
- FOWLER and GODLEY Quoted by Shaw
- FURTH, E Ein Fall von spontan entstandenen Chylothorax im Kindesalter, *Wien klin Wchnschr*, 1927, xl, 350-355
- GANDIN, S Pathogenese und Klassifikation der Milchartigen Ergüsse, *Ergebn d inn Med u Kinderh*, 1913, Bd 12, 218-326
- GRALKA, R Über Chylothorax im Kindesalter im Gefolge einer Hodgkin'schen Krankheit, *Fortschr d Med*, 1922, xl, 242-245
- GULLBRING, A Ett fall av chylothorax, *Hygeia, Stockholm*, 1918, lxxx, 840-846
- GUNDER, R Ein Fall von Chylothorax, *Inaug Diss Munchen*, 1913
- HENDRICKS Quoted by Furth
- HEPPNER, G J Bilateral chylothorax and chyloperitoncum, *Jr Am Med Assoc*, 1934, cx, 1294
- HILGENBERG, F C Ein Fall von Chylothorax beim Neugeborenen, *Monatschr f Geburtsh u Gynak*, 1929, lxxxiii, 225-228
- HOFFMAN Quoted by Bargebuhr
- HOPPE-SEYLER Quoted by Lammers
- HUSSEY, A Über Chylothorax im Kindesalter, *Jahrb f Kinderh*, 1918, xxxvii, 491-518
- HYDE, F C A case of chylothorax, *Yale Med Jr*, 1909-10, vi, 167-175
- JENNINGS, C G, and RICH, H M Report of case of chylothorax in a child, *Trans Am Pediat Soc*, 1907-08, xix, 190-192

- KAMIENSKI Quoted by Lotheissen
- KRYLOFF, E Zur Frage der eitrigen Entzündung des Ductus thoracicus, Virchow's Arch f path Anat u Phys, 1927-28, cclvii, 1-3
- LAMMERS, V Zur Kasuistik des nichttraumatischen Chylothorax, Inaug Diss Borna-Leipzig Buchdruckerei, Robert Noske, 1910
- LEE, F C The establishment of collateral circulation following ligation of the thoracic duct, Johns Hopkins Hosp Bull, 1922, xxxiii, 21-31
- LEIDHCKER Quoted by Bargebuhr
- LESCHTSCHINSKI Quoted by Furth
- LEWIN, P Chylothorax, report of a case, Am Jr Med Sci 1916, cli, 71-83
- LION Quoted by Shaw
- LOFFLER Quoted by Furth
- LOTHEISSEN Über Chylothorax Wien klin Rundschau 1907, xvi, 5-7
- LYTTER, J C Chylous ascites and chylothorax, Med Clin N Am, 1927, vi, 479-486
- MARTIN Quoted by Bargebuhr
- McFARLAND, J A fibrous tumor of the receptaculum chyli, Trans Path Soc, 1893-95, xii, 204-207
- MILTON, J P A case of chylothorax, with a record quantity of fluid withdrawn from left pleural cavity and ultimate recovery, Brit Med Jr, 1907, ii, 1210
- MINASSIANZ, Y Un cas de suppuration du canal thoracique et d'Adeno-phlegmon sus-claviculaire consecutif a un cancer du pylor, 8°, Paris Theses, Paris, 1927 (Menchaca-Minot)
- MONALDI, T DFS Carcinomatosi secondaria del dotto toracico, Riforma Medica, 1933, xiv, 1284-1285
- MORTON Quoted by Bargebuhr
- MORTON Quoted by Lammers
- MOUCHET, A Le chylothorax traumatique, Jr de Chir, 1933, xli, 386-399
- MUNK Quoted by Lewin
- NEUENKIRCHEN Ein Fall von Chylothorax, St Petersburger Med Wehnschr, 1890, vii, 459-462
- OBERNDORFER, S Atherosklerose des Ductus thoracicus, Verhandl d deutsch path Gesellsch, 1925, xx, 247-252
- OMEROD-WILK Quoted by Bargebuhr
- OPOLZER Quoted by Lammers
- OTTO Quoted by Boegehold
- PAPPENHEIMER, P Über eitrige Entzündung des Ductus thoracicus, Virchow's Arch, 1921, ccxvii, 274-289
- PATTON, N Quoted by Lewin
- PISEK, G R Report of a case of chylothorax, Trans Am Pediat Soc, 1917, xxx, 144-147
- QUINCKE Quoted by Bargebuhr
- REICHENBACH Quoted by Bargebuhr
- REME, G Doppelseitiger Chylothorax und Spontanpneumothorax bei einem 3 jährigen tuberkulösen Kinde, Monatschr f Kinderh, 1926, xxxiv, 135-138
- RENNERS Quoted by Lammers
- ROSIN Quoted by Lammers
- ROTMANN Über fetthaltige Ergüsse im den grossen serösen Hohlen, Ztschr f klin Med, 1896-97, xxxi, 416-442
- RUELLELL, K R Chylous ascites and chylothorax due to lymphogranulomatosis of the mesentery and the receptaculum chyli, Indianapolis Med Jr, 1927-28, xxx, 213-215
- RUST Quoted by Boegehold
- SALE, L Chylothorax, report of a case, Interstate Med Jr, 1912, xiv, 50-54
- SARGENTE Quoted by Furth
- SCHRAMM Quoted by Furth
- SENATOR Quoted by Furth

- SHAW, H B Milky effusions occurring in serous cavities, with report of a case of chylous ascites and chylous hydrothorax, Jr Path and Bact, 1899-1900, vi, 339-355
- SHIFRMAN, DE W H Chylothorax in children, Arch Pediat, 1907, xiv, 646-658
- STINER, P Chylothorax duplex, Chylopericardium und Ascites Chylosus bei einem Fall von fibroser Pleuritis und Ausgedehnter Fibrose bei der Lungen, Beitr z Klin d Tuberk, 1932, lxxvi, 757-773
- STEWART, C A, and LINNER, H P Chylothorax in the new born infant, report of a case, Am Jr Dis Child, 1926, xxi, 654-656
- STRASSER Quoted by Lammers
- STRAUSS, H Über Chylothorax tuberculosus nebst Beiträgen zur chemisch-mikroskopischen Diagnostik pathologischer Ergüsse, Charite Ann, 1920, xvi, 89-105
- STUART, W J Operative injuries of the thoracic duct in the neck, Edinburgh Med Jr, 1907, xii, 301-317
- SYFERS, H W A case of chylothorax, Clin Jr, London, 1900, xvi, 278-279
- VRIESEN Chylothorax, Deutsch med Wchnschr, 1906, xxxii, 1359
- VIRCHOW Quoted by Furth
- WEIGERT Quoted by Furth
- WHITIA Quoted by Lammers
- WHITE Quoted by Shaw
- WIEHFLM Quoted by Furth
- WILLIAMSON, C S A case of chylothorax, Internat Clin, 1920, xxx, 7-20
- WINKLER and SCHWEDENBERG Quoted by Fehr
- WURM, H Zur Kasuistik der Entzündungen des Ductus thoracicus Thrombolymphangitis des Halsteils mit Hasyuenthrombose nach hamorrhagischen Lungeninfarkt, Centralbl f allg Path u path Anat, 1927, xxxix, 545-548
- ZAWADSKI Quoted by Bargebuhr

ALTERATIONS IN HEPATIC FUNCTION PRODUCED BY EXPERIMENTAL HEPATIC LESIONS

By JESSIE L. BOLLMAN, M.D., and FRANK C. MANN, M.D.,
Rochester, Minnesota

IN the course of our studies of hepatic function in the experimental animal many of our observations have appeared to be of clinical interest. While direct transposition of experimental data to clinical practice is unwise, anyone would agree that differences attributable to species are minor points compared to the major problems of hepatic disease, and that such differences will find simple explanation with complete understanding of the physiology and the pathology of the liver. It will not be necessary to call attention to the many similarities that appear in animals with experimentally produced lesions of the liver and in human beings with disease affecting that organ. The conclusions we have reached were based entirely on experimental observations, but we feel safe in saying that, under similar circumstances, they are equally true for man.

Before discussing the functions of the liver which are altered by pathologic changes in that organ, we would sharply separate two types of hepatic lesions. These two types are not the acute and chronic, although this classification would in many cases effect the same separation. Our first type is based on changes produced by injury to the cells of the liver so that their functional capacity is altered, and the second type is produced by a reduction in the number of functioning hepatic cells. In the first type many of the functions of the liver may remain, and the symptoms noted may be due partly to loss of other function and to toxemia, and to absorption of toxic material from necrotic cells in the liver. The second type is that produced by surgical removal of large amounts of hepatic tissue or by gradual removal of hepatic cells killed by toxic agents when the regenerative processes of the liver have failed. In advanced atrophic cirrhosis, some of the symptoms appear to be the result of the diminished number of cells in the liver which have been replaced by connective tissue. For the most part, however, both types of pathologic changes in the liver are present. Even in the acute hepatic necrosis produced by chloroform or carbon tetrachloride some symptoms may be attributed to the absence of hepatic function, but the chemical and metabolic changes found are not of the same magnitude as occur at death in the liverless animal². The fatal outcome following administration of these hepatic poisons must be attributed to other factors, such as the formation of toxins in the liver by the necrotizing action of the toxic agent.

The rarity of death from hepatic failure, comparable to the death of animals following complete removal of the liver, is apparent from the few re-

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935.
From the Division of Experimental Medicine, The Mayo Foundation, Rochester, Minnesota.

ports of this condition in the literature Stadie and Van Slyke and Rabnowitch have each reported cases in which the blood and urine showed changes similar to those found after complete removal of the liver of animals. Such changes as we have reported are always found in the liverless animal, so that the absence of such changes must mean that some hepatic tissue remains functioning or that some of the substances which would ordinarily disappear are being replaced by the treatment which is being employed. After complete removal of the liver and recovery from anesthesia, the animal appears normal for two to twelve hours until symptoms of hypoglycemia appear.⁹ Such symptoms are promptly dispelled by the administration of glucose, and they will not recur if sufficient glucose is given to prevent the sugar content of the blood from reaching hypoglycemic levels. If the supply of glucose is maintained, the animal will remain in apparently normal condition for many hours, usually from 24 to 56 hours. Characteristic symptoms then develop: the reflexes disappear, convulsions occur, and the animal dies. This sequence of symptoms is run in one to six hours, and we have been unable to alter this course.

Many of the chemical changes that accompany removal of the liver are very definite. There is a progressive decline in the sugar content of the blood, which cannot be reversed by methods that raise the blood sugar in normal animals, except by the administration of glucose or a few substances which in the animal organism are readily converted to glucose. Urea ceases to be formed and there is a decrease in the urea content of the blood equivalent to the amount of urea excreted in the urine.⁵ Deamination of amino acids does not occur and there is a marked increase in the amino acid content of the blood, urine, and tissues.⁷ Destruction of uric acid ceases and there is an increase in the uric acid content of the blood and urine.⁶ Jaundice occurs, with retention of bilirubin in the blood. The reaction of the retained bilirubin is "indirect" to the Van den Bergh reagent.³ If jaundice is produced by occlusion of the common bile duct or by extensive degenerative changes in the liver, the reaction of bilirubin in the serum is "direct" to the Van den Bergh reagent. Subsequent removal of the liver under these conditions further increases the bilirubin content of the blood, but the increase is only that of "indirect" bilirubin whereas the former level of "direct" bilirubin remains unchanged or decreases due to excretion of this substance by the kidneys. Complete failure of hepatic function should therefore increase the amount of "indirect" reacting bilirubin in the blood. We have not observed this in any case of hepatic failure produced by acute or chronic toxic degeneration of the liver, so that it would appear that this function of the liver is quite persistent and can be accomplished by small amounts of functioning hepatic cells.

Most of these functions of the liver may be performed completely by only a small amount of that organ.⁸ McMaster and Rous found that the hepatic bile ducts from as much as 80 per cent of the liver could be ligated without the retention of bilirubin in the blood. We have been able to remove large

portions of the liver of animals, so that less than 20 per cent remained, without permanently interfering with the excretion of bilirubin. Under these circumstances there is usually some retention of bilirubin for the first few days after operation, but this is a result of edema and other changes in the liver caused in turn by the surgical manipulation and factors connected with the operation. After recovery from these acute effects, bilirubinemia disappears and many other functions of the liver appear normal. The regulation of blood sugar, the formation of urea, deamination, the destruction of uric acid, the utilization of glucose, levulose, and galactose, and the excretion of bromsulphalein, rose bengal, and so forth, are not materially altered from what is found in the normal animal. Regeneration of hepatic tissue occurs rapidly following partial removal of the liver of normal animals,¹⁰ but normal function returns before hepatic tissue has been completely restored, and function returns similarly in animals in which restoration has been prevented. Similar retention of liver function is seen in animals with experimental cirrhosis sufficient to destroy a large portion of the liver.¹ Even in extreme conditions many of the measurable functions of the liver appear to be within normal limits.

Certain other functions of the liver appear to be more easily influenced by induced pathologic changes. Smith and Whipple have demonstrated that the liver forms bile salts. In their animals which had complete biliary fistulas the daily excretion of bile salts depended somewhat on the nature of the diet, being about 100 mg of taurocholic acid per kilogram of body weight. Fasting or feeding with sugar reduced this figure to 20 or 40 mg. Feeding liver, kidney, or beef muscle produced from 200 to 300 mg of taurocholic acid per kilogram of body weight in 24 hours. Bile salts administered by vein or by mouth were quantitatively excreted into the bile. Mild hepatic injury, such as is produced by small amounts of chloroform or by an Eck fistula, may greatly reduce the amount of bile salts formed. In these cases the reduction in the amount of bile salts formed is coincident with the injury produced in the liver, but the same is not true following phosphorus poisoning which may produce extensive lesions in the liver with but little reduction in the excretion of bile salts.

Although glycocholates and taurocholates administered by vein or by mouth are completely excreted in the bile, they are also reabsorbed from the intestine unless the bile is withdrawn as in the animal with a biliary fistula. Continued feeding of large amounts of bile salts, however, does not produce an accumulation of these substances in the body, nor are they excreted as such in the urine or feces. The liver regulates the amount of bile salts by destroying the excess and by forming more when the supply is low if the necessary materials are provided. Following ligation of the common bile duct, bile salts appear in the urine in fairly constant amounts, somewhat less than are excreted in the bile of animals with biliary fistulas. Administration of bile salts increases the bile salt content of the urine, but a considerable portion of the bile salts is destroyed. If the liver is removed completely,

all of the bile salts administered appear in the urine within a few hours, and in the absence of the liver no evidence of the destruction of bile salts is found. The role of the liver in the formation of bile salts is established by the fact that, while small amounts of administered bile salts are completely recovered in the absence of the liver, no bile salts can be detected in the blood or urine following removal of the liver unless bile salts have been administered.⁴ The fact that bilirubinemia and bilirubinuria develop in the absence of the liver again indicates the difference in the metabolic formation of bile pigment and bile salts.

With complete biliary obstruction, the dog excretes bile salts in the urine and bile salts are present in the blood. With continued jaundice and progressing hepatic deficiency, less bile salts are excreted. Additional injury to the liver by chloroform, carbon tetrachloride, or toluylenediamine further reduces the amount of bile salts in the urine to very small amounts, and markedly reduces the level of bile salts in the blood. Thus the presence of bile salts in the blood and urine of dogs with completely ligated bile ducts indicates the presence of a liver with otherwise good functional capacity, and the absence of bile salts from the blood indicates impaired hepatic function. This observation can frequently be confirmed by a decreased utilization of galactose, but we have had several cases in which the histologic picture in the liver corresponded much better with the bile salt findings than with the results of the galactose test.

The presence or absence of bile salts in the blood might appear as a good index in the troublesome problem of differentiating obstructive jaundice and intrahepatic jaundice of toxic origin. Certainly in the experimental animal such differentiation can be made if due regard is paid to the course of the jaundice. Jaundice produced in otherwise normal animals by the administration of hepatic toxins, such as chloroform, phosphorus, carbon tetrachloride, tetrachlorethane, or toluylenediamine, has certain features in common with obstructive jaundice in that bile salts are found in the blood and urine for a few days. As the animals recover, the bile salts disappear from the blood and urine, while the bile pigment is diminishing. Additional hepatic injury, by repeated administration of the toxic agent, also causes the bile salts to disappear from the blood and urine while bilirubinemia is increased by added injury to the liver. The level of bile salts in the blood of dogs with obstructive jaundice, while the liver is in good condition, is higher than that found in the jaundice produced by toxic agents.

The detoxicating functions of the liver also appear to be definitely influenced by the condition of that organ. We have not been very successful in measuring the detoxicating function of the liver by chemical methods, but biologic methods seem to be much more sensitive under the conditions we have studied. Satisfactory approximations may be made of the differences in detoxication by clinical observations of the effects of the toxic agent and the microscopic examination of the effects on hepatic tissue. Numerous experiments indicate that the systemic and local effect of many toxic agents

is dependent on the condition of the liver at the time of administration of the toxin. Marked changes occur in the chemical composition and microscopic appearance of the liver under normal conditions with relation to the taking of food. A short time after a meal the glycogen content and water content of the liver increase somewhat in proportion to the amount and nature of the food taken. Shortly after digestion is complete the glycogen content of the liver again decreases. By feeding unbalanced diets, greater changes may be made which have less daily variation. By feeding a diet rich in carbohydrate, the glycogen content of the liver may be increased from a normal of 2 to 5 per cent to about 15 per cent, and it may be raised to as much as 25 per cent by intravenous injection of large amounts of glucose. Such measures increase the water content of the liver and reduce the fat content. With excessive fat diets the fat content of the liver may be increased from 3 per cent to as much as 50 per cent of the weight of the liver, and at the same time the water content may be reduced from 72 per cent to 30 per cent and the glycogen content to 0.1 per cent. It is interesting to note that the liver is able to maintain its ordinary functions without impairment except in extreme conditions.

We have many times noted that the reaction to toxic agents, both from the viewpoint of systemic reaction and the injury produced in the liver, varied with the diet of the animal and the chemical composition of the liver. The survival time and general well-being of the animal after complete occlusion of the common bile duct are markedly improved by a diet rich in carbohydrate. Dogs survive from six to twelve months after ligation of the common bile duct if fed a diet rich in carbohydrate. Similar animals fed diets rich in protein seldom survive more than three months. Similarly, animals fed carbohydrate withstand repeated administration of carbon tetrachloride in amounts which prove fatal to those fed protein, and particularly to those on a fat diet. The diets we have used have all been adequate in maintaining the untreated animals indefinitely. The appearance of the lesions produced in the liver has also been correspondingly less in the animals fed carbohydrate. The difference in the systemic effect of tetrachlorethane is very marked, even with daily variation in the glycogen content of the liver, when the animals are fed a carbohydrate diet once daily. A small dose of tetrachlorethane (1 c.c.) produces marked intoxication and coma of six to eight hours' duration when administered 24 hours after the last feeding, at 18 hours the effect is noticeably less, and at 12 hours only a mild intoxication is noted. If the same dose of tetrachlorethane is given from one to six hours after feeding, no visible effect is noted. The lesions produced in the liver by this drug are also in proportion to its systemic effect.

We attempted to correlate the effects of carbon tetrachloride and tetrachlorethane on the liver with the marked changes produced in it by diets rich in fat and poor in carbohydrate, but we were not very successful. Small amounts of these toxic agents produced no effect when the liver was rich in

glycogen, but proved fatal within 24 hours if the liver was fatty at the time of administration. With smaller doses inconsistent results were obtained, some fat-fed animals were unaffected by amounts that were fatal to others, and the lesions in the liver likewise were not constant.

The reaction to ethyl alcohol is a good means of illustrating variations in susceptibility corresponding to the glycogen content of the liver as varied by dietary means. With the fat diet we have used there is not much change in the composition of the liver during the first week of its administration, but during the second week the percentage of fat begins to increase and the glycogen to decrease. By the third week the fat content has risen to around 20 per cent and by the fourth week to 40 per cent. Glycogen decreases in the second week to less than 1 per cent, and gradually declines to 0.2 or 0.3 per cent in the third and fourth weeks. We injected dilute alcohol intravenously to eliminate possible variations in the rate of intestinal absorption. When the glycogen and fat of the liver were normal, dogs momentarily become intoxicated with the injection of the equivalent of 1.5 c.c. of 95 per cent alcohol per kilogram of body weight, and definite intoxication of about 30 minutes' duration followed the injection of 2.0 c.c. Larger amounts proved fatal. Animals that were fed carbohydrate diets, so that the glycogen content of the liver was more than twice the normal value at the corresponding time following the meals, gave evidence of only momentary intoxication with 2 c.c. of alcohol per kilogram of body weight. The first week on the fat diet did not produce any appreciable changes, but during the second week the amount of intoxication from the same dose of alcohol was definitely increased. In the third and fourth weeks coma and intoxication, lasting from one to two hours, followed the injection of 1.5 c.c. of alcohol. In animals with 50 per cent fat and 0.1 per cent glycogen in the livers this dose usually proved fatal. Change from a fat to carbohydrate diet gradually restored the excessively fat livers to normal within a week. The tolerance to alcohol also improved and returned to normal at the same time.

It is of course true that tissues other than the liver are altered by the same measures that change the chemical composition of the liver. With the methods we have employed the changes in the liver are usually more than 10 times as great as the corresponding changes in other tissues, such as in the muscles or kidneys. In other animals after previous injury to the liver by toxic agents or by surgical measures, these other tissues are not sufficiently involved to produce detectable chemical changes, and the reaction to toxic agents again corresponds to the condition of the liver. We therefore feel justified in attributing the altered susceptibility to toxic agents which we have observed to alterations produced in the chemical composition and histologic appearance of the liver.

We have called attention to the fact that animals dying from extensive hepatic injury, regardless of the methods by which it is produced, do not show the typical symptoms or chemical changes that are found following complete

removal of the liver The detoxicating function of the liver appears to be altered by changes in the organ so that its susceptibility to toxic agents is increased Under most circumstances we feel that increased susceptibility to toxic agents is responsible for the symptoms shown, and that usually the animal succumbs before the entire function of the liver is lost At least part of the toxic substances may be of metabolic origin and are somewhat related to the autolytic disintegration of injured hepatic tissue These observations seem particularly true in animals with hepatic lesions, which do not appear to be very detrimental to the animal under ordinary conditions but which cause the animal to fail rapidly following surgical intervention that would be of no consequence to normal animals Following operation, these animals are markedly lacking in resistance and extensive degenerative changes rapidly occur in the injured liver Preoperative diets rich in carbohydrate and intravenous injection of glucose both before and after operation have enabled animals to recover under circumstances that would be fatal without the administration of carbohydrate

SUMMARY

Many of the functions of the liver may be completely performed by only a small portion of that organ Extensive injury to the liver may show little influence on such functions as the excretion of bile, regulation of blood sugar, formation of urea, deamination of amino acids, and so forth Certain other functions of the liver appear to be more easily influenced by induced pathologic changes The ability of the liver to form bile salts is easily impaired, but since the liver also destroys and excretes bile salts, no simple test involving bile salts seems capable of indicating the functional capacity of the liver However, if due regard is taken of the circumstances, the finding of bile salts in the blood of jaundiced animals indicates that the condition of the liver is otherwise good The disappearance of bile salts from the blood under these conditions indicates improvement as a result of relief from obstruction, or regression as a result of pathologic changes in the liver

The detoxicating function of the liver also seems to be impaired easily The systemic effects of several toxic agents are often roughly proportional to the extent of the abnormal chemical and histologic changes in the liver at the time of administration of the toxic agent The changes that accompany a diet rich in carbohydrate seem to increase the resistance to some toxic agents, and the depletion of the glycogen content of the liver by fat diets or other means decreases the resistance, this can be illustrated with the administration of alcohol in doses which are almost without effect on animals fed carbohydrate but which are fatal to animals fed excessive fat The alterations in susceptibility appear to be related to the glycogen content of the liver Measures directed toward increasing the glycogen content of the liver appear to be of value in reducing the systemic effects of certain toxins, and they also appear to prevent further injury to the liver

BIBLIOGRAPHY

- 1 BOLLMAN, J L Experimental cirrhosis of the liver, Atlanta Proc Interstate Postgrad Med Assoc N Am, 1928, 387-390
- 2 BOLLMAN, J L, and MANN, F C Experimentally produced lesions of the liver, ANN INT MED, 1931, v, 699-712
- 3 BOLLMAN, J L, and MANN, F C Studies of the physiology of the liver XXII The Van den Bergh reaction in the jaundice following complete removal of the liver, Arch Surg, 1932, XLIV, 675-680
- 4 BOLLMAN, J L, and MANN, F C The influence of the liver on the destruction of bile salt, Arch Path, 1933, XVI, 304
- 5 BOLLMAN, J L, MANN, F C, and MACARTH, T B Studies on the physiology of the liver VIII Effect of total removal of the liver on the formation of urea, Am Jr Physiol, 1924, LXIX, 371-392
- 6 BOLLMAN, J L, MANN, F C, and MAGATH, T B Studies on physiology of the liver X Uric acid following total removal of the liver, Am Jr Physiol, 1925, LXXII, 629-646
- 7 BOLLMAN, J L, MANN, F C, and MACARTH, T B Studies on physiology of the liver XV Effect of total removal of the liver on decamination, Am Jr Physiol, 1926, LXXVIII, 258-269
- 8 MANN, F C, and BOLLMAN, J L Liver function tests, Arch Path and Lab Med, 1926, I, 681-710
- 9 MANN, F C, and MAGATH, T B Studies on the physiology of the liver II The effect of the removal of the liver on the blood sugar level, Arch Int Med, 1922, XXX, 73-84 III The effect of administration of glucose in the condition following total extirpation of the liver, Arch Int Med, 1922, XXX, 171-181
- 10 MANN, F C, FISHBACK, F C, GAY, J G, and GRIFFIN, G F Experimental pathology of the liver III, IV and V, Arch Path, 1931, XII, 787-793
- 11 McMASTER, P D, and ROUS, P The biliary obstruction required to produce jaundice, Jr Exper Med, 1921, XXXIII, 731-750
- 12 RABINOWITCH, I M Biochemical findings in a rare case of acute yellow atrophy of the liver, Jr Biol Chem, 1929, LXXXIII, 333-335
- 13 SMITH, H P, and WHIPPLE, G H Bile salt metabolism V Casein, egg albumin, egg yolk, blood and meat proteins as diet factors, Jr Biol Chem, 1930, LXXXVII, 689-704 VIII Liver injury and liver stimulation, Jr Biol Chem, 1930, LXXXIX, 727-738 IX Eck fistula modifies bile salt output, Jr Biol Chem, 1930, LXXXIX, 738-751
- 14 STADIE, W C, and VAN SLAKE, D D The effect of acute yellow atrophy on metabolism and on the composition of the liver, Arch Int Med, 1920, XXV, 693-704

CASE REPORT

PANCREATIC LITHIASIS *

By D B FAUST, M D , F A C P , *San Francisco, California*

It is perhaps too generally accepted that pancreatic lithiasis is a rare condition. The relative paucity of reported cases is the basis for this assumption. Graef observed calculi in the pancreas for the first time in 1664. In 1932 Ackman and Ross ²⁴ reported a case which, they stated, brought the total number up to 108.

It may safely be stated that the condition either is in reality so rare that few of us are privileged to see a case or that it presents difficulties of diagnosis that have prevented its more frequent recognition. In favor of the latter supposition is the fact that most of the earlier cases were discovered at necropsy, that later the diagnosis, if made, was usually based upon the findings at surgical exploration, and that it is only in the last two decades that reliable diagnostic help has been obtainable from the roentgen-ray.

The clinical symptoms are notoriously unreliable. The condition may be asymptomatic, there may be only mild digestive symptoms, there may be symptoms not readily referable to the digestive system, or there may be severe, persistent or intermittent epigastric pain. The roentgenologic finding of radio-opaque areas suggestive of calculus in the upper abdomen may not solve the difficulty since even when these are not confused with renal or biliary calculi they may readily be interpreted as calcified retroperitoneal glands. It seems probable, nevertheless, that if in cases with mild or severe gastrointestinal symptoms due consideration be given to the possible presence of pancreatic calculi and advantage taken of all modern methods of diagnosis many more cases would be diagnosed.

The relief of many cases of pancreatic lithiasis in recent years by surgical operation and the fact that the untreated condition is often fatal, lend point to an attempt to present in tabular form a summary of the symptoms and findings in 22 of the more recent and carefully studied cases from the literature, and to the report of a case personally observed. The earlier reported cases include symptomatic data difficult to evaluate and are without laboratory or roentgenologic reports, they are therefore not included.

It is realized that the data on the cases in the foregoing table are incomplete but it is thought that all important points in the available abstracts have been included. Of the 22 cases listed, only six were in women. The youngest patient was 20 years old and the oldest 73 years of age. The most common subjective symptom was epigastric pain which often radiated to the back or shoulders. In its site or character there was nothing distinctive. Jaundice was present in some cases, but usually late, and was of no dependable diagnostic significance. Glyco-

* Received for publication April 4, 1935

† Major Medical Corps, U S Army, San Francisco, Calif

TABLE I

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
F	24	Friedrich and Hoesch ³	Epigastric pain radiating to left shoulder Palpable epigastric tumor and marked loss of weight	Presence of jaundice, glycosuria, and gall stones not stated	Positive	Yes, for pancreatic cyst Stones, found but not removed Re-covered
M	42	Mraz ⁴	Pain in epigastrium, especially on left side Fatty stools	Presence of jaundice not stated No glycosuria	Not stated	Yes Stones (45) removed Recovered
M	46	Orth ⁵	Pain in epigastrium, radiating to back Frequent vomiting and diarrhea	Presence of jaundice not stated No glycosuria	Positive	Yes One large stone removed Recovered
M	Not known	Meyer ⁶	Sense of pressure in epigastrium No pain Fatty stools	Presence of jaundice and glycosuria not stated	Positive	Yes One large stone removed Recovered
M	37	Irsigler ⁷	Epigastric pain radiating to left shoulder Loss of weight Acute attack simulating ruptured gastric ulcer requiring immediate operation In shock	Not stated Gall bladder normal	Not stated	Yes Several stones Died
M	33	d'Antona ⁸	Intermittent diarrhea and undigested food remnants Fatty stools	Urine positive for sugar Developed cardiac disease and died suddenly	Not reported	No Autopsy showed numerous stones in pancreatic duct and pancreatic parenchyma transformed into lipomatous tissue
M	51	Schondube ⁹	Symptoms of cirrhosis of liver and fatty stools Diminution of pancreatic ferments	Glycosuria present	Positive	No Autopsy confirmed diagnosis No gall stones

TABLE I (Continued)

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
F	64	Perman ¹⁰	Attacks of epigastric pain Fatty feces Jaundice, late	No glycosuria	Positive	Yes At first operation gall stones were removed and at second pancreatic stones were removed Patient died Autopsy revealed another stone in pancreatic duct and carcinoma in head of pancreas, a metastasis from carcinoma of liver
M	67	Perman ¹⁰	Attacks of severe epigastric pain Intermittent diarrhea with grayish fetid stools	Glycosuria present Jaundice developed after operation	Positive	Yes Several stones removed Patient died Autopsy revealed sclerotic changes of pancreas but no more calculi
M	67	Óhneil ¹¹	Loose, gray, offensive, frequent stools for 30 years Epigastric pain radiating to right shoulder with fatty stools last 6 months	Glycosuria present Jaundice late	Positive	Yes Several stones removed Temporary relief of symptoms Symptoms returned early and patient died Autopsy revealed another stone and scirrhous carcinoma
M	45	Wolf and Tietze ¹²	Diarrhea and loss of weight Fatty stools Slight abdominal pain just prior to passage of feces	Blood sugar normal Glucose tolerance slightly diminished	Positive	Yes Six stones removed Patient recovered
M	46	Zukschwerdt ¹³	Colicky abdominal pain for 8 years After a blow on epigastrium he had severe epigastric pain and vomited blood	Blood sugar 140 mg Gallbladder operation 8 years previously No stones Tumor palpated at this time to right of median line but not investigated	Positive for cyst of pancreas with numerous stones	No Patient refused operation Case not confirmed by operation or autopsy but believed confirmed by presence of mass at exploratory operation and subsequent roentgen-ray

TABLE I (Continued)

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
F	20	Choy and Oh ¹⁴	None mentioned	Urinary retention, dyspnea, edema of legs, and "indigestion"	Not stated	No Died one month after admission Autopsy confirmed nephritis Also numerous pancreatic calculi Stones consisted of calcium carbonate
M	56	Quenu ¹⁵	Severe hematemesis and melena	None stated	Positive At autopsy pancreas roentgen-rayed again and showed same shadows	No Patient died before operation was attempted Autopsy showed stones of calcium carbonate with traces of phosphates Source of hemorrhage could not be found
M	53	Fliessinger and Olivier ¹⁶	Typical symptoms of cirrhosis of liver	None stated All symptoms over-shadowed by those of advanced cirrhosis of liver	Not stated	No Autopsy showed marked cirrhosis of liver and pancreas and numerous stones in pancreas
M	Not stated	Soupault ¹⁷	Pain in epigastrium, recurrent, with vomiting and slight fever Tumor in epigastrium, soft and slightly painful	After second operation developed high blood sugar, requiring diet and insulin	First picture indicated cyst of pancreas Another after second operation showed a chain of stones in duct of Wirsung	Yes First operation cyst drained At second operation two stones found At third operation several stones removed Died 36 hours after last operation, from embolus Autopsy showed additional stones in duct of Wirsung
F	35	Dillon ¹⁸	None	Had diabetes 3½ years prior to death Later developed pulmonary tuberculosis which caused death	Not stated	No Autopsy showed numerous stones plugging the ducts with atrophy of tail of pancreas

TABLE I (Continued)

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
M	56	Graham Hodgson ¹⁹	Substernal pain radiating to back for 6 months. Two days before examination, severe vomiting	None	Positive	Yes Pancreatic stone found No further details given
F	73	Collins ²⁰	Severe intermittent epigastric pain radiating to back and left side of abdomen. Tenderness in epigastrium more marked on left side	No glycosuria or jaundice	Positive	Yes Single stone removed from tail of pancreas and, also, numerous gall stones removed Died three days later
M	72	Villery Radot, Miget, and Gauthier-Villars ²¹	Mild attacks epigastric pain and pain in right iliac fossa for 2 years. Intermittent diarrhea, anorexia, and marked loss of weight last 2 months. Abdominal pain more continuous but never severe. Vomited blood once. Fatty stools containing blood	No glycosuria	Not stated	No Autopsy showed carcinoma of liver with cirrhosis. Also multiple stones of pancreas with fatty degeneration of parenchyma of pancreas
F	58	Billaudet ²²	Epigastric pain intermittently for many years radiating to lower border liver and right shoulder accompanied by nausea. Last 8 years pain more continuous but less severe and no radiation. Stools normal	No glycosuria or jaundice	Positive. Picture of gall stones and pancreatic stone the latter more dense	Yes One stone in pancreas removed. Also gall bladder containing several stones, removed. Pancreatic stone consisted of calcium carbonate and phosphate and some magnesium phosphate
M	45	Quanu ²³	Attacks of epigastric pain radiating to back and becoming more frequent and severe. Loss of weight moderate	None stated	Positive after operation	Yes Large mass in head of pancreas considered carcinoma or chronic pancreatitis. Subsequent roentgenograms showed pancreatic stones. Symptoms became less severe. No operation attempted

suria was noted in a minority of the cases. The examination of the abdomen in these patients was usually negative. In acute attacks, however, moderate rigidity was usually noted. Occasionally, but seldom, an upper abdominal mass was felt.

These symptoms and physical findings must be interpreted with due regard to the fact that in pancreatic lithiasis there is frequently an associated cholelithiasis, and that cirrhosis of the liver and pancreatic cyst are likewise often found present. There is very little speculative comment in the reports of the cases summarized



FIG 1 Film after barium enema showing numerous dense shadows across entire epigastrium

above as to the nature of these relationships except for the reasonable supposition that blockage of the pancreatic ducts by stones may lead to the formation of pancreatic cysts.

Such laboratory studies as have been reported have not been of great diagnostic help. Leukocytosis was encountered in only a few cases. Studies of the pancreatic juice contributed nothing of value. The presence of fatty stools, however, was frequently observed and might be considered suggestive. Chemical

analysis of the calculous material was reported in only a few instances, the results showed the presence of calcium carbonate with or without calcium phosphate and magnesium phosphate

The greatest diagnostic help in these cases has been derived from roent-



FIG 2 Gastrointestinal series showing deformed and enlarged duodenal arc with numerous opaque densities in the epigastric region

genography The pancreatic stones cast shadows which are usually, according to the reports, denser than those which may be produced by gall stones The interpretation of the roentgen findings presents some difficulties Gall stones

and renal calculi can usually be excluded by pyelograms and cholecystograms. The differentiation from calcified retroperitoneal or mesenteric glands, and from calcifications in the abdominal aorta or in abdominal aneurysms, may not give such definite results. The localization of the site of the calculus by fluoroscopy and films from lateral and oblique angles may rule out aortic involvement. Preceding the gastrointestinal series a swallow or two of barium viewed under the fluoroscope in oblique or lateral position may determine whether the shadow is in front of, or in rear of the bowel. Mention is made of the value of the gastro-



FIG 3 Pancreas, stomach and duodenum removed en masse. Pointer indicates fistulous tract between pancreas and greater curvature of the stomach. A few of the calculi lying in dilated pancreatic duct are shown.

intestinal series in outlining distortion in the normal arc of the duodenum.

The following is an abstract of a case admitted to the Gastrointestinal Section of Letterman General Hospital, San Francisco, California. I believe this case is unusually interesting because it showed probably the most extensive involvement ever reported. The entire pancreas was involved and stones of all sizes were too numerous to count or even estimate. Stevens, in "The Practice of Medicine," (3d Edition, 1932) states "The most common sequel to pancreatic lithiasis is

chronic interstitial pancreatitis which sometimes reaches an advanced grade. The ducts of the gland are almost invariably dilated and occasionally true retention cysts are found. Fistulous communications with stomach or duodenum have been reported. Abscess and carcinoma are rare associations." This case

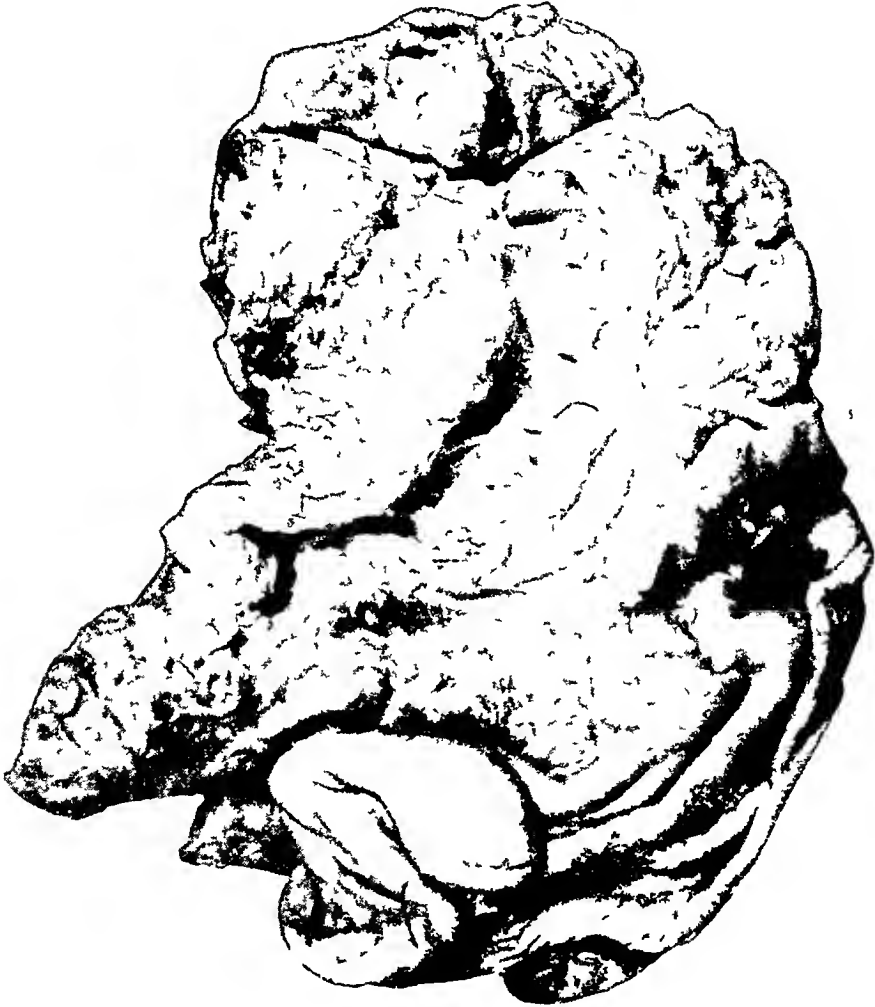


FIG 4 Same specimen shown in figure 3. Note enormous size of pancreatic duct. Stones can be seen obstructing some of the smaller ducts.

is unusual in that it revealed the presence of all these complications except cysts and carcinoma.

CASE REPORT

The patient was a laboring man, 45 years old, a native of California. He formerly drank alcoholics excessively but only moderately in recent years. Arthritis

afflicted the left shoulder four years before. He has had numerous fractures as a result of injuries sustained in horse races. He denied all venereal diseases.

Present Illness Symptoms referable to the gastrointestinal tract have been present for 10 or 12 years with apparent increasing severity. *Heartburn* for 10 years has appeared usually about 30 minutes after breakfast and again about 10 p.m. There is partial relief by the use of alkalis. *Pain* in the region of the umbilicus has appeared about one hour after meals. It has usually lasted about 30 minutes and has



FIG 5 Roentgen-ray of pancreas, stomach and duodenum after removal en masse at autopsy showing innumerable calculi involving the entire pancreas

been rather severe, subsiding later to an almost continuous dull ache in the epigastric area. *Nausea* has been present frequently but *vomiting* has been rare. *Gaseous distention and eructation* have been present continuously. *Hematemesis* has been noted only once, about two years ago, when the vomitus contained about a teaspoonful of bright red blood. *Melena*. The patient believed he had passed tarry feces many times. The *appetite* has been poor for the last eight years.

The patient stated there have been frequent remissions when he was comfortable and able to work, only to be followed by a recurrence. There has been no history of jaundice or of clay colored feces, or of constipation or diarrhea. The teeth are in poor condition, many of them have been extracted. For years he has lived on a soft diet for this reason and also to prevent attacks of epigastric pain. On September 27, 1934, he developed severe pain in the epigastrium that "doubled him up." Because of these symptoms and the presence of muscular rigidity a tentative diagnosis of ruptured duodenal ulcer was made and he was admitted to the hospital.

On examination he was emaciated, weighing only 96 pounds. The skin was dry and warm, systolic blood pressure 110, diastolic 60. The abdomen was distended and there was marked tenderness over the umbilical region and in the left epigastrium with moderate rigidity. A mass could not be palpated.

Laboratory Findings Repeated urinalyses were negative throughout. The blood count, repeated many times, was entirely normal except for the leukocyte count which varied from 7,200 (polymorphonuclear cells 76 per cent) to 19,400 (polymorphonuclear cells 91 per cent) just prior to the operation.

The blood Wassermann test was negative. On a prostatic smear many pus cells were seen.

Gastrointestinal roentgenograms showed that the arc of the duodenum was widened and that there were clusters of opaque bodies in this region extending to the left of the median line. The chest roentgenogram was negative. There was no air beneath the dome of the diaphragm.

The temperature ranged from normal to 101° F.

After obtaining the history, completing the physical examination and viewing the roentgenograms my impression was that he had either a peptic ulcer, or a carcinoma of the pancreas with calcified glands in the same region.

We could not proceed further with the study of the case due to the severe attacks of abdominal pain. The attacks by this time were very severe and would appear almost every hour. Food could no longer be tolerated. He was operated upon on October 8, 1934. The pancreas was markedly enlarged from head to tail and fluctuated. Pus was aspirated from which the colon bacillus was recovered. Crepitation was also noted in the pancreas. Drainage in two stages, with 48 hours intervening, was instituted.

The postoperative course was unfavorable and death occurred October 14, 1934, six days after operation. There had been no signs of generalized peritonitis nor was there apparent postoperative pneumonia or other lung involvement.

At autopsy, except in the area of the drainage tract leading from the skin wound down to the head of the pancreas, there was no increase of fluid in the peritoneal cavity. The serous surface was smooth and shining. Stomach, pancreas, and duodenum were removed together. The pancreas was very large and felt like the crop of a chicken, full of gravel and stones. The duodenum was negative. The stomach was negative except for an opening in the wall posteriorly on the greater curvature about 10 cm from the pyloric ring. This opening was about 1 cm in diameter with smooth, round edges that were not indurated. The stomach at this point was adherent to the pancreas by a plastic membrane that could be separated with little difficulty. There was pus in a little sac formed between the stomach and pancreas, suggesting a fistulous tract. The pancreas at this point was deeply pitted. Pus escaped through the fistulous tract from the pancreas on little pressure. The pancreas was opened from the ampulla. The opening of the main pancreatic duct was not evident to the eye on close inspection but just inside the opening the duct was dilated irregularly in places to as much as 3.5 cm. Much pus drained from this dilated duct and from the dilated branches leading into it. The wall of the main duct was thick and gray. There were no erosions or areas of softening. The pancreas as a whole, except for its resemblance to a "bag of gravel," was firm. The pus flowing from the dilated

ducts suggested an empyema rather than a suppurative pancreatitis. Many stones were lying in the dilated main duct, and others were lying in the dilated branches. These stones were as large as 1.3 by 0.9 by 0.7 cm and were rough, with numerous projections, some suggesting coral formations. Several hundred stones were estimated to have been found. On analysis they were made up of calcium carbonate and calcium phosphate.

Microscopic examination of the pancreas shows evidence of progressive chronic pancreatitis of long standing, with many areas of calcium deposit. The arteries show marked endarteritis. The parenchyma appears to be much reduced. Superimposed is an acute suppuration involving not only the epithelium lining the ducts but also large areas of the gland tissue. The weight of the pancreas was not obtained as the stomach, duodenum, and pancreas were preserved en masse.

SUMMARY

A case of pancreatic lithiasis is reported. Several hundred calculi involving the entire parenchyma as well as the ducts were found at necropsy.

Most of the usual, as well as the unusual, sequelae from pancreatic calculi involving the pancreas and adjacent organs, as reported by other observers, were noted.

Subjective symptoms, physical examination, and laboratory findings are so variable and unreliable that they afford little aid in differentiating this condition from the more common disorders encountered in the upper abdomen.

Greater accuracy in diagnosis will result if pancreatic lithiasis be given proper consideration in the study of any patient complaining of acute or chronic abdominal distress. Careful study of roentgenograms will undoubtedly result in more frequent recognition of this condition.

BIBLIOGRAPHY

- 1 STEVENS, A. A. The practice of medicine, 3d edition, 1933, W. B. Saunders Co., Philadelphia, Pennsylvania, p. 571.
- 2 SENNETT, S. N. Pancreatic lithiasis, *Brit. Med. Jr.*, 1933, ii, 3-5.
- 3 FRIEDRICH, H., and HOESCH, K. Röntgenologisch nachgewiesene Steine in einer Pankreaszyste, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1927, xxi, 334-337.
- 4 MRAZ, G. Pankreassteine, *Zentralbl. f. Chir.*, 1926, lxx, 3217-3218.
- 5 ORTH, O. Exstirpierter Pankreasstein, *Zentralbl. f. Chir.*, 1927, lxx, 1220-1223.
- 6 MEYER, A. W. Pankreasstein, *Zentralbl. f. Chir.*, 1928, lxi, 2440-2441.
- 7 IRSIGLER, F. J. Pankreassteine und intraabdominelle Blutung, *Zentralbl. f. Chir.*, 1931, lxxviii, 2006-2016.
- 8 D'ANTONA, L. Zur Lithiasis und Lipomatosis der Bauchspeicheldrüse, *Ztschr. f. klin. Med.*, 1929, cxl, 147-166.
- 9 SCHONDUPE, W. Ein intra vitam diagnostizierter Fall von Pankreassteinen, *Röntgenpraxis*, 1931, iii, 1095-1099.
- 10 PERMAN, E. Two cases of concretions in the pancreas, *Acta chir. Scandinav.*, 1926, lxi, 23-29.
- 11 OHNELL, H. Lithiasis et cancer pancreatitis, *Acta med. Scandinav.*, 1929, lxxxi, 10-20.
- 12 WOLF, G., and TIETZE, A. Zur Röntgendiagnostik der Pankreassteine, *Klin. Wchnschr.*, 1928, vii, 1182-1184.
- 13 ZUKSCHWERT, L. Röntgenologisch geklarter Fall von Pankreassteinen und Pankreaszyste, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1929, xxxix, 469-471.
- 14 CHOY, P. D., and OH, H. Y. A case of pancreatic stone, *China Med. Jr.*, 1931, xlv, 54-58.

- 15 QULNU, J Lithiase pancréatique, Bull et mem Soc nat de chir, 1933, lix, 832-834
- 16 FIFSSINGER, N, and OLIVER, H R Sur un cas de lithiase du pancreas, Bull et mem Soc med d hop de Paris, 1933, xlix, 1389-1391
- 17 SOUPAULT Hydro-pancreatose calculeuse, Bull Acad de med, 1933, cx, 161-167
- 18 DILLON, E S Pancreatic calculi with glycosuria, Proc Path Soc Philadelphia, 1924-1925, xxxii, 37-39
- 19 GRAHAM HODGSON, H K X-ray diagnosis in case of pancreatic calculus, Brit Jr Radiol, 1932, v, 783
- 20 COLLINS, H A Pancreatic lithiasis, report of case, Jr Iowa Med Soc, 1934, xxiv, 277-280
- 21 VALLERY-RADOT, P, MIGET, A, and GAUTHIER-VILLARS, P Lithiase et adipose du pancreas associees, Bull et mem Soc med d hop de Paris, 1933, xlix 1118-1123
- 22 BILLAUDFT, G Lithiases vesiculaire et pancreatique concomitantes, Bull et mem Soc nat de chir, 1933, lix, 446-453
- 23 QULNU, J Un cas de lithiase diffuse du pancreas, Bull et mem Soc nat de chir, 1927, liii, 204-208
- 24 ACKMAN, F D, and ROSS, A Pancreatic lithiasis, Surg, Gynec and Obst, 1932, lv, 90-95

EDITORIAL

POSTURE AND BLOOD PRESSURE

THE physiologic responses of the circulatory system to changes in posture were first studied in animals by Hill and Barnard¹ in 1897. They found, by placing a dog in the vertical position, feet down, and cutting the cervical portion of the spinal cord, that the pressure in the aorta dropped to zero and most of the blood was collected in the splanchnic region. By squeezing the abdomen the aortic pressure returned to normal. Hill and Barnard also demonstrated that if rabbits raised in a hutch were placed in a vertical position, feet down, the animals would die in a very short time unless a tight abdominal binder was applied. The drop in blood pressure with change to the vertical position was attributed to a deficient vasomotor tone, associated with lack of tone of the abdominal wall.

In man, as early as 1905 Crampton^{2, 3} studied and established the normal changes in blood pressure and pulse rate with change in posture. He considered that the alterations in blood pressure and pulse rate which occurred with change from the horizontal position to the vertical one were a measure of vasomotor tone as related to the splanchnic vessels. He developed an ingenious statistical arrangement for evaluating bodily fitness in terms of rise in blood pressure and drop in pulse rate and vice versa. This test was often applied to determine the physical fitness of athletes.

This work was seemingly overlooked for a time, with but an isolated worker here and there studying the effect of change in posture on blood pressure and pulse rate. Mortensen,⁴ studying healthy young women, attributed the rise in systolic blood pressure not to vasomotor tone but to myocardial response to the effects of gravity and to muscular activity coincident with change of position. Likewise, Turner⁵ studied the abnormal response of blood pressure to change in posture in apparently normal persons. He felt that, because of excessive loss of circulatory minute volume, anemia of the brain occurred and that this caused symptoms of dizziness and fainting on prolonged standing. An abnormal fall in systolic pressure alone was found most frequently in cases of myocardial degeneration. An abnormal fall in diastolic pressure alone was considered indicative of deficient vaso-

¹ HILL, L., and BARNARD, H. The influence of the force of gravity on the circulation, part 2, *Jr Physiol*, 1897, **xxi**, 323-353.

² CRAMPTON, C. W. A test of condition preliminary report, *Med News*, 1905, **lxxxii**, 529-535.

³ CRAMPTON, C. W. The gravity resisting ability of the circulation, its measurement and significance (blood ptosis), *Am Jr Med Sci*, 1920, **clv**, 721-737.

⁴ MORTENSEN, M. A. Blood pressure reactions to passive postural changes. An index to myocardial efficiency, *Am Jr Med Sci*, 1923, **clv**, 667-675.

⁵ TURNER, A. H. The adjustment of heart rate and arterial pressure in healthy young women during prolonged standing, *Am Jr Physiol*, 1927, **lxv**, 197-214.

motor tone, uncompensated by efficient abdominal and thoracic muscular action. This would result in congestion of the splanchnic circulation even though the myocardium were functionally intact.

In 1925, a new interest in the subject was awakened by the description of the clinical entity, postural or orthostatic hypotension, by Bradbury and Eggleston.⁶ The essential characteristics of the syndrome, according to these authors are (1) a sharp drop in systolic and diastolic blood pressure with syncopal attacks on change of posture from the recumbent to the upright position, (2) no increase in the pulse rate with this drop in blood pressure, (3) anhidrosis, associated with intolerance to heat during the summer months, (4) a larger volume of urine excreted at night than in the daytime. A possible explanation, as given by Bradbury and Eggleston, was a deficiency or paralysis of the myoneural junctions. At this time no successful treatment was established. It was not until 1928 that a satisfactory treatment was discovered by Ghrist and Brown,⁷ when it was shown that the oral administration of ephedrine sulphate would maintain the blood pressure when the subject was in the upright posture. These workers concluded that the essential disturbance in the disease was the lack of resistance in the splanchnic vessels to shifts in the blood mass and absent or diminished vagus regulation of the cardiac rate to changes in the blood pressure.

In contrast to the above stated hypotheses, a group of English workers have suggested that, since the predominant afferent impulses responsible for the production and control of postural tone are proprioceptive, and arise in the muscles of the extremities, the lower limbs play an important part in the mechanism of postural hypotension. MacWilliam⁸ maintains that the increased fall in blood pressure and rise in pulse rate, with the change in position of the patient from the sitting to the standing position, are attributable to the position of the limbs. Otherwise, the trunk is in the vertical position under both conditions and therefore the effect cannot be attributable to the direct effect of gravity on the splanchnic region. However, Crampton has stated that the splanchnic circulation is kept within bounds by the support received from the flexed position of the sitting posture.

Henderson⁹ has expressed the belief that there is another important factor in circulatory efficiency, which he calls the "venopressor mechanism." This factor chiefly determines the venous return to the right side of the heart. The venopressor mechanism consists of the mechanical effect of the general tonus of the bodily musculature, and more especially the tonus of the abdominal muscles and particularly of the diaphragm, as well as of the non-

⁶ BRADBURY, S, and EGGLESTON, C. Postural hypotension, a report of three cases, *Am Heart Jr*, 1925, 1, 73-86.

⁷ GHRIST, D. G., and BROWN, G. E. Postural hypotension with syncope: its successful treatment with ephedrine, *Am Jr Med Sci*, 1928, clxxv, 336-349.

⁸ MACWILLIAM, J. A. Postural effects on heart-rate and blood-pressure, *Quart Jr Exper Physiol*, 1933, xxiii, 1-33.

⁹ HENDERSON, Y. The volume of the circulation and its regulation by the venopressor mechanism, *Jr Am Med Assoc*, 1931, xcvi, 1265-1269.

striated muscles of the alimentary canal which all exert an effect on the contents of the splanchnic veins

Following extensive anterior rhizotomy, with complete resection of the pre-ganglionic fibers that go to make up the splanchnic nerves, in patients with hypertension, two conditions are produced (1) a denervation of the splanchnic vessels, and (2) relaxation of the abdominal wall. There is a rather striking similarity between these patients and the group with postural hypotension. The decrease in blood pressure is considerably greater when the subject is in the upright position than when he is recumbent. Occasionally, the decrease in blood pressure on standing is sufficient to produce syncope. This tendency is only temporary in most instances and may be remedied by the wearing of a tight abdominal binder. The level of blood pressure at which syncope occurs is generally much higher than in the patients with postural hypotension, but the latter group maintains a much lower level of blood pressure in the recumbent position. An interesting observation was made in one patient with an advanced, organic form of hypertension. Following section of all the intercostal nerves on both sides, no significant change in the blood pressure occurred with change to the upright position. The conclusion may be drawn that the relaxation of the intercostal and abdominal muscles alone was not sufficient to disturb the blood pressure in this instance, and that the vasomotor system plays the predominant rôle in the decrease of blood pressure in the upright position.

Up to the present, eighteen cases of postural or orthostatic hypotension have been reported, with almost as many theories for the etiology of the disease. There may be a phylogenetic basis for this failure in the support of blood pressure in the ascent of man from the four-legged animal to the upright one. Since the group as a whole contains individuals with certain inadequacies, it is probably a measure of fitness. The fact that epinephrine and ephedrine, drugs which act on the myoneural junctions, produce rises in blood pressure, suggests that these structures are functioning, in part at least. The sharp drop in blood pressure in the upright posture demonstrable in the cases of hypertension in which operative interruption of the splanchnic innervation has been carried out is strong evidence that the vasomotor mechanism plays a definite rôle in all instances of postural hypotension.

G R

BOOK REVIEWS

Diseases of the Nervous System By W RUSSELL BRAIN, M A , F R C P (London)
xvi + 899 pages, 15.5 × 22.5 cm Oxford University Press, London 1933

In recent years the field of neurology has been intensively cultivated by many who were not primarily neurologists the bacteriological studies of the various forms of encephalomyelitis, the surgical attack upon tumors of the brain and cord, upon certain diseases of the peripheral nerves and upon intractable pain, and the physiological and clinical studies of the interrelationship of the autonomic system and of the endocrines with bodily structure and visceral function, all these and other developments have greatly added to the scope of neurology and altered our conception of the relative importance of the various neurological disorders

Dr Brain has achieved in this volume an exceptionally well balanced and lucid account of the present status of clinical neurology This is in large part due to his skillful arrangement of the material After an introductory section of 116 pages on disorders of function in the light of anatomy and physiology, the diseases of the nervous system are discussed in seventeen further sections They are grouped according to practical clinical relationships rather than forced into apparently logical subdivisions The grouping is sometimes anatomical, as in the section on the cranial nerves, sometimes etiological as in the section on the infections of the nervous system and sometimes functional as in the section entitled "Hydrocephalus and Intracranial Tumor" Sections frequently are opened by a brief chapter on the anatomical and physiological data necessary to an understanding of the diseases later described Frequently also a chapter will be devoted to topical discussion as, for examples, those devoted to Headache, to Compression of the Spinal Cord, and to the Late Effects of Head Injuries These features in the arrangement of the material add greatly to the practical usefulness of the volume to the clinician

The author has succeeded in including a brief but usually adequate discussion of even the most recently differentiated neurologic syndromes or diseases and has drawn freely on the American and Continental literature of both neurology and internal medicine The references given are well selected

The point of view is conservative, at times a little dogmatic perhaps because of the requirements of brevity The book is unusually readable because of its clear, easy style It appears to be a very desirable textbook for students and it will prove of equal or greater value to the internist for quick reference and also as a means of bringing him abreast of the advances in modern neurology

M C P

Diabetes Mellitus and Obesity By GARFIELD G DUNCAN, M D xii + 227 pages,
14 × 20.5 cm Lea and Febiger, Philadelphia 1935 Price, \$2.75

In this small volume an attempt has been made to give the general practitioner and the student a working knowledge of the two metabolic diseases with which he will most commonly have to deal, diabetes mellitus and obesity The subject matter is condensed, the stress is laid on practical methods of treatment The greater portion of the work is devoted, rightfully, to diabetes and to its complications The subject of obesity is only briefly considered An appendix contains useful food tables and weight scales

Chapter 8 contains an excellent outline of the procedures followed with diabetic patients in the Metabolic Clinic, "B" service and ward at the Pennsylvania Hospital It will be of interest and of value to all those concerned in organizing adequate treatment of such cases

This clearly written short monograph will be of value to many physicians who have wanted something more than a diet manual and something briefer than a long treatise

J S E

Hospital Organization and Management By MALCOLM T. MACEachern, M.D., C.M., D.Sc. 944 pages, 17 × 25 cm Physicians' Record Co., Chicago, Ill. 1935 Price, \$7.50

This volume is extraordinary in its completeness and will undoubtedly be of great value to hospital administrators as a reference book. Its general usefulness is widened also by the fact that it deals not only with purely administrative hospital problems but also discusses at great length the various problems peculiar to each professional department. The book contains a great deal of material that should be of as much interest to the physician in chief, director of nurses, dietitian, chief engineer, and others as to the administrators themselves.

Dr. MacEachern of course is well known in the field of hospital administration and has put the results of many years of study into his book. The arrangement of material is extremely concise in that each step in planning a new organization is taken up in the logical order, from the organization of the governing body to the actual opening and dedication of a functioning hospital. One of the most interesting characteristics of the book is that the material presented is such that it is made applicable to all types and sizes of institutions with no neglect of detail which is peculiar to one or another sort of hospital.

M L S

Fifty Years of Medicine and Surgery By FRANKLIN H. MARTIN. 449 pages, 14 × 21.5 cm. The Surgical Publishing Company of Chicago, Chicago, Ill. 1934

This volume, which was issued a very short time before the author's death, contains a very readable account of his interesting career. Dr. Martin was a man of strong personality who often bent men and events to conform with his will. It is still early to appraise his achievements as an Editor and in connection with the development of the American College of Surgeons and the role it has played in elevating the standards of surgery and of hospitals in this country. There is no doubt, however, that this book will always prove an interesting document in the study of the medical history of a period during which its author was a living force.

M C P

Principles and Practice of Physical Diagnosis By PAUL MARTINI, translated from the Italian by Robert S. Loeb. 213 pages. J. B. Lippincott Co., Philadelphia. 1935. Price, \$2.00

Dr. Martini's textbook is pocket size, brief and concise. It contains a summary of the principles underlying physical examination. It gives the essential findings in the common pathological conditions of the chest and abdomen. The accessory aids in diagnosis, roentgenology and electrocardiography, are brought in from time to time in order to give the reader a more complete grasp of the subject. At times there seems to be a tendency to over-simplification of points that are in reality obscure. It is essentially an undergraduate textbook.

T C W

COLLEGE NEWS NOTES

AMERICAN BOARD FOR THE CERTIFICATION OF INTERNISTS

By resolution adopted by the Board of Regents of the American College of Physicians on April 30, 1935, and by resolution adopted by the Section on the Practice of Medicine of the American Medical Association on June 14, 1935, a committee consisting of nine members, six from the American College of Physicians and three from the Section on Medicine of the American Medical Association, will meet at Philadelphia, December 14, to discuss ways and means whereby an examining board, comparable to such boards existing in certain specialties, may be set up for the purpose of certification of specialists in Internal Medicine. The personnel of the Committee, as appointed by the American College of Physicians and by the Section on Medicine of the American Medical Association, is as follows:

Walter L. Bierring (A M A), Chairman of the joint Committee

David P. Barr (A C P)

Reginald Fitz (A M A)

Ernest E. Irons (A M A)

Jonathan C. Meakins (A C P)

William S. Middleton (A C P)

John H. Musser (A C P)

O. H. Perry Pepper (A C P)

G. Gill Richards (A C P)

The expenses of the Board will be underwritten by the American College of Physicians until met by fees of candidates.

The Board is not concerned with the problem of the use to which its certification may be put by the American College of Physicians in selection of Associates or Fellows.

The Board's first responsibilities will consist of determining upon the plan for examination, the character of examination and how and when the examinations shall be given.

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr.—1 reprint,

Dr. Ronald L. Hamilton (Fellow), Sayre, Pa.—4 reprints,

Dr. Arthur A. Herold (Fellow), Shreveport, La.—1 reprint,

Dr. Martin J. Synnott (Fellow), New York, N. Y.—1 reprint,

Dr. Frederick H. Foucar (Associate), Washington, D. C.—1 reprint,

Dr. William G. Leaman, Jr. (Associate), Philadelphia, Pa.—4 reprints,

Dr. W. K. Purks (Associate), Vicksburg, Miss.—7 reprints,

Dr. Frank A. Trump (Associate), Ottawa, Kan.—2 reprints

Dr. Horace P. Marvin (Associate), Captain, Medical Corps, U. S. Army, has been transferred from duty at the Station Hospital, Schofield Barracks, Hawaii, to Fort Bragg, N. C. He is at present pursuing postgraduate work in Internal Medicine at the University of Minnesota (Mayo Foundation), and will report to Fort Bragg in February, 1936.

Dr William Nimeh (Fellow), Mexico City, Mexico, was lately elected a Fellow of the Society for the Advancement of Gastroenterology, a member of its Council and foreign collaborator on its Review for Mexico

Dr Edward G Hubel (Fellow), Colonel, Medical Corps, U S Army, was retired from active service on August 31. He has been appointed an Instructor in the School of Public Health of Harvard University, Department of Preventive Medicine and Epidemiology

Twenty-eight Fellows and four Associates participated either as speakers or clinicians on the program of the Eighth Annual Graduate Fortnight of the New York Academy of Medicine, October 21 to November 2

The annual Graduate Fortnight is conducted on some subject of outstanding importance in the practice of medicine or surgery, and consists of meetings at the Academy, coordinated clinics in selected hospitals and a large scientific exhibit. This year the program was devoted to diseases of the respiratory tract

Dr William Henry Walsh (Fellow), Hospital Consultant of Chicago, recently conducted a study of the needs and plans for a new hospital to be erected through PWA funds to replace the old Erlanger Hospital in Chattanooga, Tenn

The Eighth District Medical Society of North Carolina, embracing ten counties, held a recent meeting at Greensboro, N C, the meeting being largely attended. One of the outstanding features of the program was an address by Dr E J G Beardsley (Fellow), Associate Professor of Medicine at Jefferson Medical College of Philadelphia and Governor of the American College of Physicians for eastern Pennsylvania. His subject was "A Physician's Opportunities and Responsibilities." Dr D W Holt (Associate), Greensboro, President of the Society, presided. Dr Roy C Mitchell (Fellow), Mount Airy, N C, is the District Governor of the Society. Dr Wingate M Johnson (Fellow), Winston-Salem, N C, presented an interesting paper on "Some Observations and Impressions about Influenza." "Asthma in Children" was another interesting paper presented by Dr S F LeBauer (Associate), Greensboro. Dr J P Leake (Fellow), Medical Director of the Department of Epidemiology of the U S Public Health Service, presented a discussion on poliomyelitis and a resume of the recent epidemic in that section

Dr Charles R Drake (Fellow) was recently elected President of the Minneapolis (Minn.) Board of Education

Dr John Richards Aurelius (Fellow), St Paul, Minn, has been elected Vice-President of the Minnesota Radiological Society

Dr William Branch Porter (Fellow), Professor of Medicine at the Medical College of Virginia, Richmond, spent a part of the past summer in San Juan, P R, pursuing investigative work on the blood flow in cases of anemia, his experiments being conducted at the University Hospital of the School of Tropical Medicine, the Municipal Hospital and Mimiya Clinic

Dr Joseph A Mendelson (Associate), Major, Medical Corps, U S Army, has been elected President of the newly organized Tientsin Medical Society in Tientsin, China

Dr Robert U Patterson (Fellow), Major General Medical Corps, U S Army, retired September 1 as Surgeon General of the U S Army to become Dean of the University of Oklahoma School of Medicine and Superintendent of the University Hospital

During the World War, in recognition of his services abroad, Dr Patterson received the Distinguished Service Medal and other citations for "gallantry in action"

Dr George W Covey (Fellow), Lincoln, Nebr, is President-Elect of the Nebraska State Medical Association Dr George L Pinney (Fellow), Hastings, Nebr, is a Vice-President and Dr Homer Davis (Fellow), Genoa, Nebr, is a Councillor

Dr John N Simpson (Fellow), Dean of the Medical Faculty of the West Virginia University School of Medicine since 1902, recently retired with the title of Dean Emeritus Dr Edward J Van Liere (Fellow), Professor and Head of the Department of Physiology, has been appointed Acting Dean

Dr William Lloyd Sheep (Fellow), Lieutenant Colonel, Medical Corps, U S Army, has been appointed Chief of the Medical Service and Commanding Officer of the Army and Navy General Hospital, Hot Springs National Park, Ark

Dr Hugh A Beam (Fellow), Moline, Ill, is Medical Director of the Rock Island County Tuberculosis Sanatorium, this appointment having begun on August 1

Dr Albert D Foster (Fellow), of the U S Public Health Service, has been transferred from the Medical Directorship at the U S Marine Hospital at Chelsea, Mass, to a corresponding position at the U S Marine Hospital, Portland, Maine

Dr Martha Tracy (Fellow), Dean of the Woman's Medical College of Pennsylvania, Philadelphia, has been granted a year's leave of absence Dr Henry D Jump, Philadelphia, will be the Acting Dean during her absence

Drs Henry L Bockus, Russell S Boles and B B Vincent Lyon, of Philadelphia, Max Einhorn, of New York City, Sara Jordan and Franklin W White, of Boston, and William Gerry Morgan, of Washington, D C, all Fellows of the College, were among those appointed by the Department of State of the United States Government as delegates from the United States to the First International Congress of Gastroenterology at Brussels, during the past August

Dr J K Williams Wood (Associate), Willow Grove, Pa, has been elected President of the Lehigh Valley Medical Association

Dr C Howard Maicy (Fellow), Pittsburgh, Pa, is President of the Pennsylvania Tuberculosis Society, and also President of the Pittsburgh Academy of Medicine

Dr William S Middleton (Fellow), for some years Professor of Medicine at the University of Wisconsin Medical School, has been appointed Dean, to succeed the late Dr Charles R Bardeen

Drs Richard A Kern, T Grier Miller and Charles C Wolferth (Fellows), Philadelphia, have been promoted to professorships in clinical medicine, and Dr Truman G Schnabel (Fellow), Philadelphia, to Associate Professor of Medicine on the faculty of the University of Pennsylvania School of Medicine

Dr John T Fariell, Jr (Fellow), Philadelphia, has been appointed assistant professor of roentgenology and roentgenologist of the Department of Anatomy of the Jefferson Medical College of Philadelphia

Dr Walter L Treadway (Fellow), Washington, D C, is a member of the faculty appointed at George Washington University School of Medicine in connection with its new four-year integrated curriculum in public health teaching, to parallel its curriculum in mental health established three years ago under Dr William A White (Fellow), Washington, D C

Dr George B Eusterman (Fellow), Rochester, Minn, Dr Walter Freeman (Fellow), Washington, D C, Dr Bernard Fantus (Fellow), Chicago, Ill, and Dr Ernest E Irons (Fellow), Chicago, Ill, were among the speakers selected by the Iowa State Medical Society for its graduate course on general therapeutics conducted in Davenport from September 13 to November 15

Dr Coy C Carpenter (Fellow) has been appointed Assistant Dean of Wake Forest College of Medicine, Wake Forest, N C Dr Carpenter has been Professor of Pathology at this institution for some time

Dr Enrique Koppisch (Associate), San Juan, P R, is on a Rockefeller Foundation Fellowship at Basel, Switzerland, studying filtrable viruses

Dr Rafael Rodriguez-Molina (Associate), San Juan, P R, is at the University of Chicago pursuing courses in hospital management and administration

Dr Max Pinner (Fellow) has recently resigned his position as Associate Director, in charge of the laboratories of the Desert Sanatorium, Tucson, Arizona, in order to accept the appointment by the New York State Department of Health as

Principal Diagnostic Pathologist to be in charge of the laboratories of the three New York State Tuberculosis Hospitals in Mount Morris, Ithaca and Oneonta. From November 1 on Dr Pinner's headquarters will be at Oneonta until the Herman Biggs Memorial Hospital at Ithaca is completed

STATE MEETING OF ILLINOIS MEMBERS OF THE COLLEGE AT SPRINGFIELD

Members of the American College of Physicians of Illinois outside of Chicago held a very successful regional meeting on September 24 at Springfield. A brief medical program was presented in the late afternoon. A paper by Dr Horace W Soper and Dr J W Thompson on "Combined Medical and Surgical Management of Gastric and Duodenal Ulcer, with Emphasis on the Management of Gastro-Duodenal Hemorrhage" was read by Dr Thompson. After conclusion of the discussion the members met at dinner.

Dr Ernest B Bradley, President-Elect, and his associate, Dr Walter S Wyatt of Lexington, Kentucky, were guests at the meeting and their presence was very much appreciated by the Fellows. Dr Nathan S Davis III of Chicago presented cordial greetings from the members of the College in Cook County. Major Eugene G Remartz (Fellow), now stationed at Chanute Field, represented our membership in the military services.

The sentiment of the Fellows of the College as freely expressed at the close of the dinner was that the meeting had afforded them a pleasurable opportunity for closer acquaintance and that they were enthusiastically in favor of continuing such a regional meeting as an annual event.

SAMUEL E MUNSON,
Governor for Southern Illinois

OBITUARY

DR STEWART VERNON IRWIN

Dr Stewart Vernon Irwin of Oakland, California, died suddenly in San Francisco on July 1, 1935. Death was due to coronary thrombosis. He had been advised to take a long rest from his professional duties and was about to carry out this advice, when the final attack came. Dr Irwin was born in Oakland and received his early education in the San Francisco Bay region, graduating from the University of California, with the degree of B S, in 1911. He attended Johns Hopkins University Medical School, receiving his degree of M D in 1915. During the next five years he served as assistant resident and resident physician at the Johns Hopkins Hospital.

In 1920 he came to Oakland, specializing in Internal Medicine. He became physician-in-chief of the Providence Hospital. Dr Irwin served under Professor Llewellys Barker, while at the Johns Hopkins Hospital, and became imbued with a sympathetic interest in the psychic aspects of internal medicine, which interest he maintained successfully throughout his medical career. Somewhat reserved in personality, Stewart Irwin was a brilliant thinker and a sound diagnostician. He was elected to Fellowship in the American College of Physicians on December 20, 1931.

ERNEST H FALCONER, M D , F A C P ,
San Francisco, Calif

ANNALS OF INTERNAL MEDICINE

VOLUME 9

DECEMBER, 1935

NUMBER 6

THE HEMODYNAMICS OF THE CIRCULATION IN HYPERTENSION*

By J MURRAY KINSMAN, M D, F A C P, and JOHN WALKER MOORE,
M D, F A C P, *Louisville, Kentucky*

IN the past 50 years, and especially in the last 10 years, many investigators have been studying what may be called the mechanics or the dynamics of the circulation. The physiologists have succeeded in clearing up many disputed points in their work on animals, the clinicians have solved, by purely clinical observation, many of the problems which have arisen, and the physiologists and the clinicians together have studied many of the questions involved, by experimentation on human beings. Of the mass of information thus acquired concerning the dynamics of the circulation in man, much represents isolated and seemingly unrelated facts, some of it represents correlated information concerning many factors and their interrelationships. But confusion still exists, and this confusion arises from several sources: (a) lack of correlation in the study of separate functions, (b) lack of accurate methods of measuring some of the most important of these functions, (c) lack of uniformity in respect to the conditions under which the observations were made, and (d) an apparent failure on the part of many investigators to appreciate that there may not always be any constant relationship from individual to individual, among the various functions concerned.

Within the past 10 years, relatively accurate methods of measurement of many of these functions have been developed. The velocity of blood flow, for example, can now be measured with great accuracy by several methods. The venous pressure is capable of measurement by the direct method to a degree of accuracy sufficient for our purposes. The vital capacity has been known as a very accurate index of the efficiency of the circulation for many years. The measurement of the cardiac output or blood flow is, however, still a controversial subject. Many methods have been

* Read by title at the Philadelphia meeting of the American College of Physicians, May 2, 1935.

From the Department of Medicine, University of Louisville School of Medicine, Louisville, Ky.

developed for application to the human, most of them depending upon re-breathing for their performance. Between these individual methods there is not complete agreement in the order of the figures obtained. With all these rebreathing methods, accurate results are not possible in the presence of severe congestive failure, so that although unquestionably accurate in other conditions, their field of usefulness has been limited by this drawback. Hence, a complete understanding of the hemodynamics of the circulation in heart disease in all the various states of compensation and decompensation has not been possible because of this limitation.

With the development of the dye injection method of measuring the cardiac output, we believe we have a method which accurately measures the circulation, even in the presence of severe congestive failure. We present here a study, based on this method, of the hemodynamics of the circulation in hypertension, with data concerning the changes that occur in its various functions as congestive failure develops, even to an extreme degree, and as compensation becomes reestablished. We shall also show the relative effects upon these functions of rest alone and of rest and digitalis.

The technique of the dye injection method and the evidence for its accuracy have been reported elsewhere¹. Briefly the principle of the method is as follows. A dye (brilliant vital red) is injected rapidly into a vein while simultaneously samples of blood are collected from an artery (femoral) into little tubes arranged around the outside of a rotating drum. The samples are timed and the concentration of dye in each successive sample is determined colorimetrically. From the resulting curve of concentration plotted against time the cardiac output is calculated by a simple formula.

Figure 1 shows a series of curves obtained in this fashion. In this figure are shown a typical curve obtained from a normal case, one from a case of hyperthyroidism, one from a typical cardiac case severely decompensated and one from a typical cardiac case previously severely decompensated but compensated at the time the test was made.

By this method we can determine (1) the appearance time (A T or P C T) of the dye, which indicates the pulmonary circulation time plus the time required for the dye to get to the heart from the point of injection and from the heart to the point of sampling, (2) the cardiac output (F) in liters per minute, (3) the total blood volume (B V), (4) the amount of blood (V) actively circulating in the heart and lungs and the great vessels of the chest. In addition, while the experiments were being carried out, we measured routinely (5) the vital capacity (V C), (6) the venous pressure (V P) and the blood pressure and the pulse rate. From these data we also calculated, (7) the stroke volume (S V), (8) the work of the heart (W), (9) the work per beat (W_B), and (10) the volume clearance index (V C I). This is the term we have given to a figure which is obtained by dividing the actively circulating blood volume by the stroke volume and which indicates the number of heart beats theoretically required to clear the heart, lungs and great vessels of their contained blood.

Clinically our cases were divided as follows (a) 44 cases with normal cardiovascular systems, which furnished standards for comparison, (b) 75 cases of hypertension subdivided in the following fashion (1) uncompensated (14 cases) which had never shown any signs or symptoms of congestive failure, (2) decompensated, subdivided into slightly decompen-

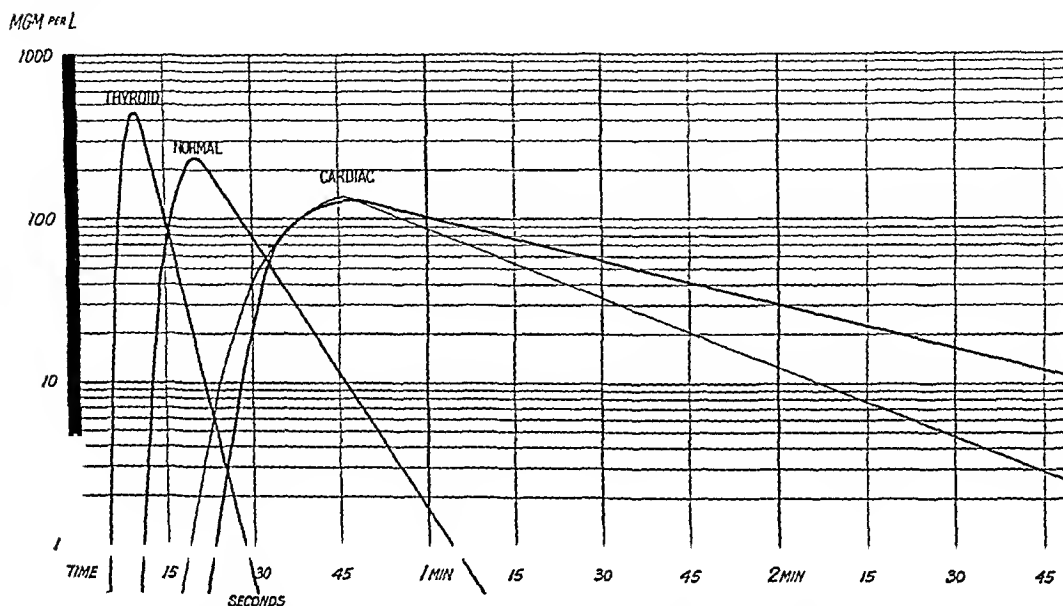


FIG 1 Illustrating typical curves obtained in different clinical conditions. Of the two curves to the right, the one in heavier lines was obtained from a cardiac patient showing severe congestive failure, and the one in lighter lines from a patient who had been severely decompensated but who, at the time the test was made, had regained compensation

sated (18 cases), moderately decompensated (7 cases), and severely decompensated (15 cases), depending upon the clinical impression as to the severity of congestive failure, (3) compensated (21 cases) which had previously been decompensated but which at the time of the test were perfectly compensated. Many of the cases in the latter group had previously been in the decompensated group. It should be noted that this classification was made from the clinical standpoint alone, before the results of the test were known.

Results The results of these tests are shown in table 1 and in figures 2 and 3. Figure 2 and table 1 both demonstrate the overlapping of results, indicating that, as has been pointed out by Starr, a single individual test on any given patient may not be of much value in diagnosis due to the fact that some of the factors may fall within the normal zone.

It will be seen from a study of figure 3 that very definite and consistent changes occur as heart failure develops and progresses. In those cases which have never been decompensated the venous pressure shows a definite increase over normal, and the vital capacity is very considerably reduced. The appearance time, that is the velocity of blood flow, is not significantly

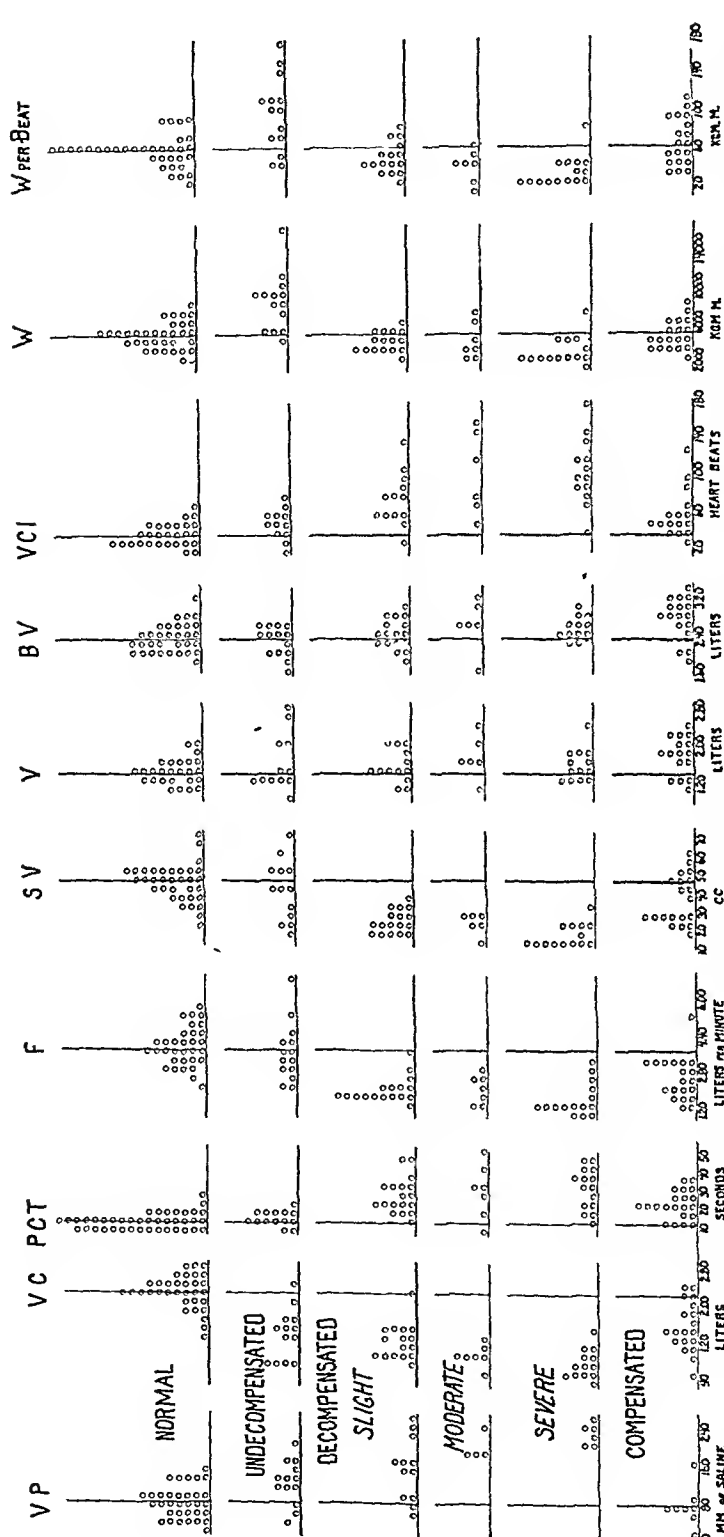


FIG 2 Illustrating the distribution of the individual figures, showing the overlapping which prohibits any specific measurement alone in any specific case from having diagnostic significance. Each circle represents a separate measurement on a different case, the number of circles in any zone representing the number of cases. The limits of the zones are indicated by the numbers below, which refer to the appropriate units. The letters above are explained in figure 3 and in the text. The vertical lines represent the normal median value for the function.

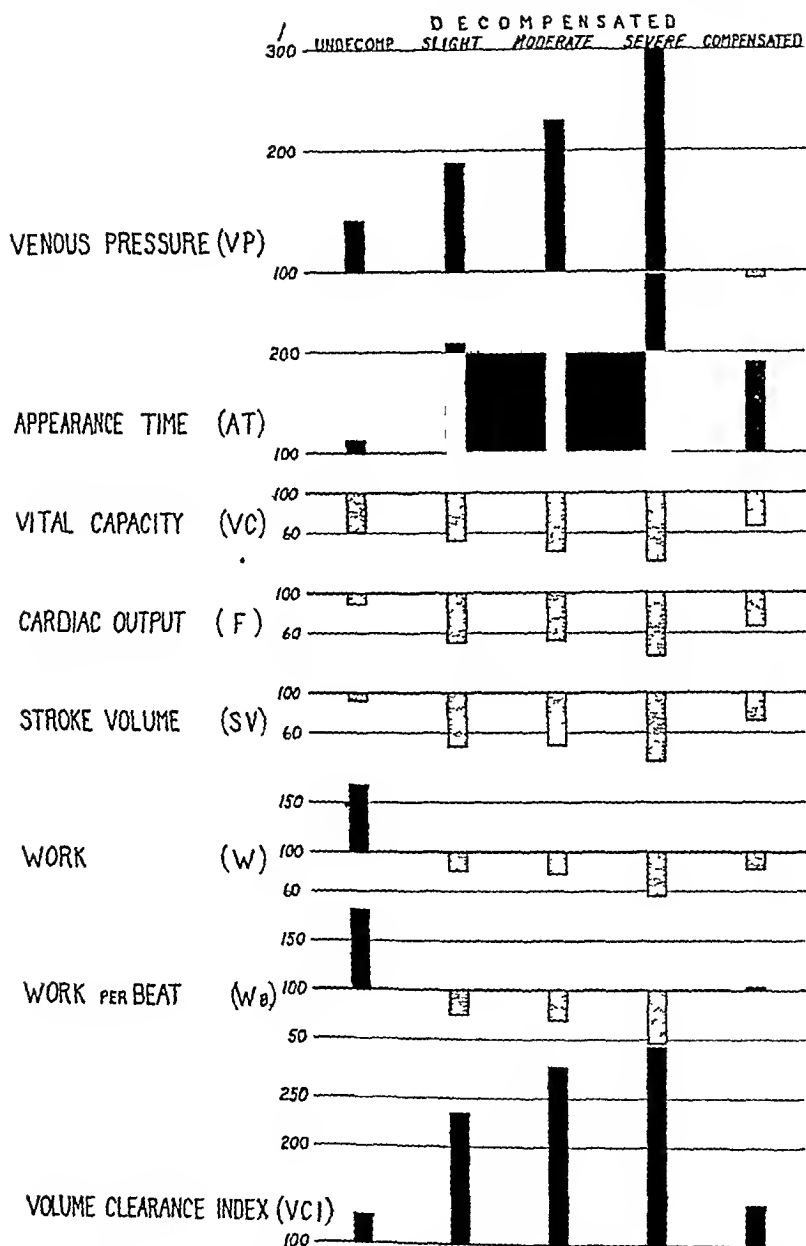


FIG 3 Illustrating the difference in terms of percentage, from the normal. The median value of each function in each group is compared with the median value for the normal group, which is expressed as 100 per cent. The heavy solid bars represent an increase in value over the normal, and the stippled bars a decrease below the normal.

changed, however, nor is there any significant change in output and the stroke volume. The volume clearance index does not show a marked increase, though there is a moderate one. On the other hand the work of the heart shows a tremendous increase, as might be expected, since the flow is essentially normal but the blood pressure greatly increased.

When congestive failure appears, however, very definite changes occur

TABLE I

The range of figures, the median and the percentage of the normal median, for each group. The groups were classified clinically before the results of the test were known. All figures are reduced to terms of surface area excepting the venous pressure, the appearance time and the volume clearance index, this applies also to table 2 and to the figures

	Normal 42 cases			Undecom- pensated 15 cases			Decompensated				Compensated 21 cases	
							Slight 18 cases		Moderate 7 cases		Severe 15 cases	
	Ex- tremes	Me- dian		Ex- tremes	Me- dian		Ex- tremes	Me- dian	Ex- tremes	Me- dian	Ex- tremes	Me- dian
Venous Pressure (V P) (mm)	20 150	75 (100%)		30 203	113 (151%)		56 275	156 (208%)	184 250	187 (249%)	203 261	240 (320%)
Vital Capacity (V C) (L)	1.35 3.01	2.31 (100%)		0.72 2.42	1.41 (61%)		0.78 2.31	1.20 (52%)	0.46 1.36	0.94 (41%)	0.37 1.54	0.71 (31%)
Appearance Time (A T or P C T) (Sec)	5.7 26.0	12.0 (100%)		6.2 20.0	13.6 (113%)		13.5 48.3	25.1 (209%)	9.5 54.5	32.1 (267%)	13.5 49.0	33.3 (277%)
Cardiac Output (F) (L/min)	2.37 5.59	3.89 (100%)		2.01 6.88	3.46 (89%)		1.41 3.99	1.93 (50%)	1.25 2.97	2.04 (52%)	1.07 3.20	1.42 (37%)
Stroke Volume (S V) (cc)	23.0 70.7	46.5 (100%)		18.6 74.0	43.0 (92%)		16.3 36.6	21.4 (46%)	11.2 26.0	22.0 (47%)	11.3 33.0	11.3 (31%)
Volume of Blood in Heart and Lungs (V) (L)	1.07 2.15	1.45 (100%)		0.99 2.85	1.36 (94%)		1.10 2.17	1.57 (108%)	1.00 2.57	1.64 (113%)	1.25 2.41	1.61 (111%)
Total Blood Volume (B V) (L)	1.89 3.25	2.40 (100%)		1.77 2.75	2.42 (101%)		1.93 3.34	2.50 (104%)	1.63 3.31	2.66 (111%)	2.20 3.04	2.59 (108%)
Volume Clearance Index (V C I) (Heart Beats)	18.9 69.7	33.0 (100%)		19.0 71.6	42.8 (130%)		29.2 133.1	77.4 (235%)	40.5 157.0	92.9 (282%)	37.8 172.0	100.1 (303%)
Heart Work (W) (Kgm M)	2410 8430	5165 (100%)		5340 16280	8665 (168%)		2530 6320	4175 (81%)	2740 6950	3970 (77%)	1950 4785	2955 (57%)
Heart Work per Beat (W _B) (Kgm M)	29.0 63.0	63.0 (100%)		40.6 104.8	104.8 (165%)		28.1 47.1	47.1 (75%)	17.9 13.2	13.2 (20%)	35.8 85.5	65.5 (100%)

The venous pressure rises and the vital capacity falls (both long known by clinical observation), the rate of blood flow slows, as shown by the increased appearance time, the cardiac output and the stroke volume both decrease to only one-half of the normal value, while at the same time the number of heart beats required to clear the heart and lungs of actively circulating blood (volume clearance index) becomes more than doubled. The work of the heart becomes reduced, not only to normal but below it, in spite of little alteration in blood pressure.

As congestive failure increases, the changes in these functions become progressively more and more marked. When decompensation has become very severe, the venous pressure has risen to more than three times the normal level and the vital capacity fallen to one-third of normal, the blood is flowing only about one-third as rapidly as before congestion appeared, the cardiac output and the stroke volume have become reduced to about one-third of the normal figure, while it now requires three times the normal number of beats to clear the heart and lungs of blood, and the heart work has been reduced to one-half of its normal value.

When compensation again becomes fully established, as a result of appropriate therapeutic measures, very interesting changes occur. As can be observed clinically, the venous pressure returns to normal, but the vital capacity does not, remaining instead at a level approximately one-third below. The rate of blood flow increases, but does not even approach the normal velocity, remaining about one-half as rapid as normal. Neither do the cardiac output and stroke volume return to normal, but remain at about two-thirds of the normal value. The number of heart beats required to clear the heart and lungs of blood also remains increased at more than 40 per cent above the normal figure. The heart work, however, again becomes normal or nearly so though it does not reach the level it did before heart failure set in.

We stated earlier in the paper that we also measured the total actively circulating blood volume and the volume of actively circulating blood in the heart and lungs and great vessels. The changes in these functions are not particularly marked, as may be seen by a study of table 1 and figure 2. It is very interesting, however, that the changes which do occur are strikingly parallel for the two. In general, it may be said that before congestive failure develops, there is no essential change in either, as congestion develops they both increase, becoming slightly greater as congestion increases. As compensation becomes reestablished, they increase greatly and significantly (to 134 per cent and 120 per cent respectively, of the normal value).

A comparison was made in these cases between the effects of rest alone and rest plus digitalis on these various functions. The result of this appears in figure 4 and table 2. It will be noted that, although rest alone produces a change toward normal in all of the functions, yet this change is not nearly as striking as occurred after digitalis was administered. Many

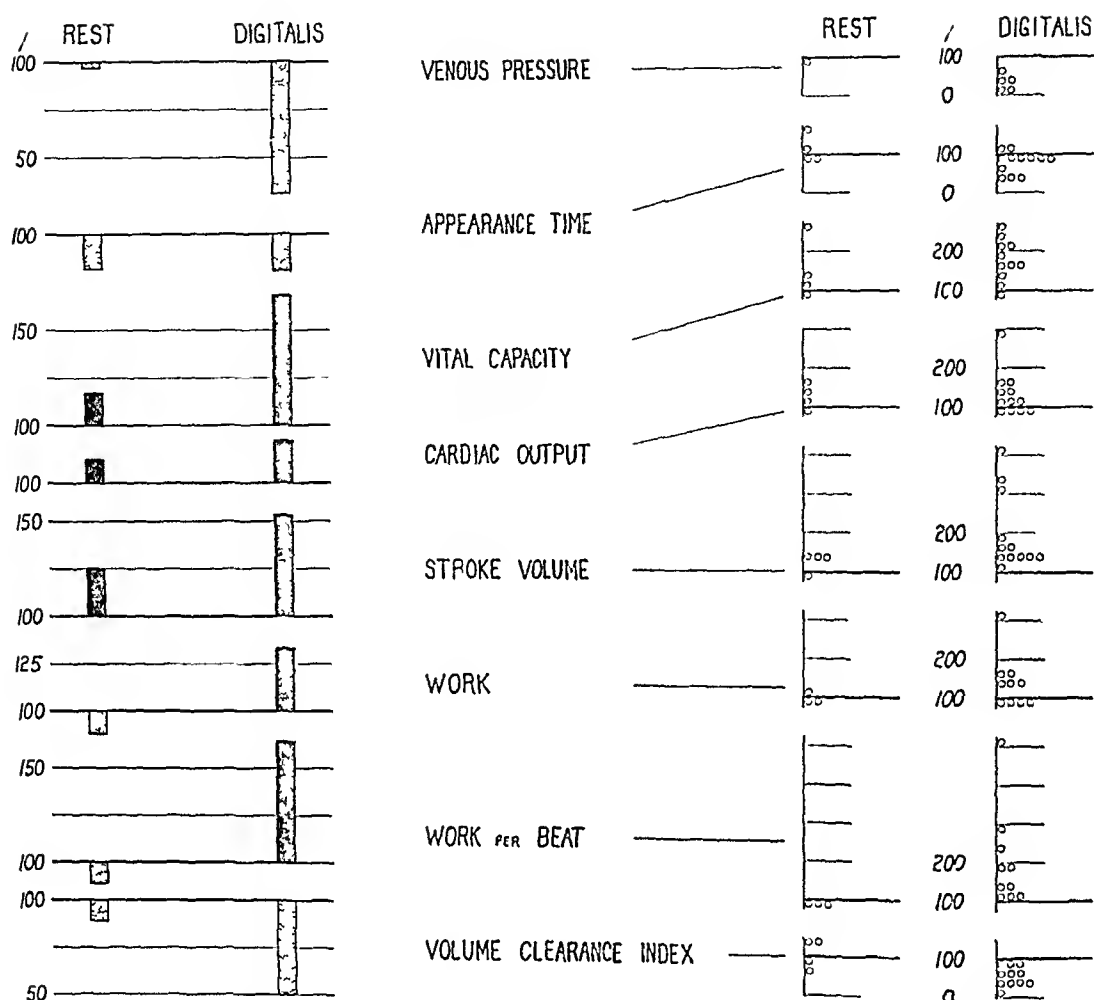


FIG 4 Illustrating the comparative effects of rest alone and of rest plus digitalis on the various functions of the circulation in congestive failure. The horizontal heaviest lines represent the previous (decompensated) median level for the group as a whole, and is taken as 100 per cent. The height or depth of the bars represents the percentage change from that previous level. The medians are taken in all instances. The right half of the figure shows the distribution of the percentile changes from the decompensated levels, each circle representing, as in figure 2, an individual case, and the changes being divided into zones.

of these patients had bed rest for as long as two weeks between the determinations, giving the circulation ample opportunity to readjust itself without help, if it could do so. The right-hand side of figure 2 represents the distribution of the individual cases in regard to the various functions outlined.

DISCUSSION

The observations reported here, concerning many of the functions of the circulation, are not new. The progressive increase in venous pressure and decrease in vital capacity as congestive failure develops have been known clinically for many years. The slowing of the blood flow under these conditions has been assumed for a long time and was demonstrated con-

clusively by Blumgart and by ourselves as far back as 1927². So, too, observations concerning the cardiac output, unreliable though they are considered by some, have been in keeping with our own. But we feel that a correlated picture of all of these functions, observed in a series of cases large enough to be considered of significance, can give us a more complete picture of what happens to the circulation as a whole, than grouping together observations on one or only a few of the many functions of the circulation. This assumes especial significance when we consider variations in individual cases. A perusal of figure 2 will illustrate this to some extent by the evidence of overlapping of results shown there. It must be remembered that we have dealt here with groups, showing the tendencies exhibited by such groups as a whole. But it must not be assumed that each individual case behaves always as the group characteristically does.

For example, in four cases picked from the severely decompensated group (see table 3), case 161 with the lowest vital capacity of all had the quickest appearance time and the highest output, whereas case 182, with a vital capacity nearly three times as great, had the slowest appearance time and the lowest output, though the venous pressure was the same in both cases, and case 90 with the highest vital capacity of all, had an appearance time and an output intermediate in position. Thus throughout all of our observations we encounter many variations, where sometimes, for example, the flow may be normal and the velocity of blood flow decreased, or vice versa. Therefore, it is apparent that not the observation of one or two or three functions only, but the measurement of all of them simultaneously will give us the true picture of the circulatory state in any given individual.

Starr³ has shown that in normal persons there is a linear relationship (within limits) between heart work and heart volume, that as the heart volume increases the heart work increases also, whereas in congestive failure the increase in heart volume and the decrease in heart work throw this relationship outside the normal zone. We have taken teleroentgenograms on most of our patients, and although we have not yet analyzed the results, it is apparent that the coordinates of work plotted against volume are far outside the normal zone. In this respect our results agree perfectly with those of Starr, although his method of determining heart work is based on rebreathing.

The lack of marked changes in the volume of blood in the heart, lungs and great vessels might cause one to assume that our method of measuring this factor was at fault since it is obvious from both clinical and postmortem experience that the lungs and great vessels do become engorged with blood as congestive failure develops. However, it must be borne in mind that we are measuring only the actively circulating blood, and that stagnant blood is not accounted for. Though the change is not great, there is a decided tendency for even the actively circulating blood in the heart, lungs, etc. to become increased as congestion develops, moreover, the changes in the volume

TABLE II

The effects of rest alone and of rest plus digitalis upon the various cardiac functions studied. In each group of three figures, the first represents the figure obtained when first tested, while decompensated, the second the figure at a later date, after rest or digitalis, and the third the percentile change of the second figure from the first. The figures at the foot of the columns represent the median percentile change in that group for the function in question. The state of compensation is represented as o, fully compensated, +, +, +, +, +, slightly, moderately and severely decompensated respectively. The letters above are explained in table 1.

Rest

Case No	State of Compensation	V P mm	V C L	A T Sec	F L/min	S V c c	V L	B V L	V C I H B	W Kgm M	W _B Kgm M
23	++ +		0.71 0.86 +21%	16.5 13.5 -18%	2.83 3.99 +41%	20.0 26.6 +33%	1.66 1.55 -8%	2.20 2.48 +13%	84.6 57.9 -32%		
31	++ o		0.46 1.27 +76%	43.8 32.8 -25%	1.64 2.55 +56%	21.0 29.0 +38%	2.06 2.35 +14%	3.31 2.95 -11%	111.7 82.6 -16%	3235 3225 ±0%	41.5 35.8 -14%
73	++ +	184 178 -3%	0.94 0.88 -6%	17.5 19.8 +13%	2.79 2.30 -18%	26.0 21.0 -13%	2.16 1.62 -25%	2.58 1.93 -25%	61.4 77.4 +26%	6950 5755 -17%	64.4 58.1 -10%
40	+ o		1.28 1.50 +17%	15.5 25.8 +66%	3.14 3.53 +12%	36.0 45.0 +25%	1.05 1.86 +77%	2.35 2.13 -9%	29.2 41.6 +42%	6320 5185 -18%	71.8 65.6 -9%
		-3%	+19%	+3%	+27%	+29%	+3%	=10%	+5%	=17%	-10%

Digitalis

16	++ +		0.50	41.5 20.3 -51%	1.32 1.63 +24%	14.0 22.0 +57%	1.76 1.10 -38%	2.67 2.00 -25%	128.6 50.3 -61%	2780 4210 +51%	28.7 53.2 +85%
24	++ +		0.83 1.21 +46%	36.6 31.0 -15%	2.44 2.30 -6%	21.0 30.0 +25%	2.41	3.01		4480 3660 -18%	41.8 48.1 +7%
53	++ +	250 140 -41%	0.73 1.40 +92%	24.3 25.3 +4%	1.42 1.41 -1%	13.5 16.0 +19%	1.39 1.57 +13%	2.71 2.89 +7%	101.9 97.1 -4%	2955 2530 -14%	28.2 28.1 ±0%

TABLE II—Continued

Digitalis

Case No	State of Compensation	V P mm	V C L	A T Sec	F L/min	S V cc	V L	B V L	V C I H B	W Kgm M	W B Kgm M
25	++ o		1.13 1.85 +64%	33.2 31.8 -4%	1.53 2.32 +52%	13.0 42.0 +223%	1.47 2.36 +61%	3.03 3.35 +11%	111.9 55.4 -50%	2705 3785 +40%	24.2 68.8 +184%
47	++ o		0.53 1.11 +109%	18.0 16.2 -10%	1.55 2.06 +33%	14.3 27.0 +89%	1.34 1.09 -19%	2.44 2.15 -12%	94.4 40.4 -57%	2970 2915 -2%	27.5 39.4 +43%
83	++ o	210 70 -67%	0.92 1.98 +115%	47.7 14.7 -69%	1.07 3.23 +201%	11.3 46.8 +314%	1.94 1.34 -31%	2.50 3.04 +22%	172.0 28.7 -83%	1950 6415 +220%	20.5 93.0 +420%
135	++ o	230 15 -93%	0.54 1.23 +128%	35.9 28.8 -20%	1.35 2.11 +56%	16.8 25.1 +49%	1.88 2.35 +45%	2.34 2.31 -1%	112 93 -17%	2440 3300 +35%	30.5 39.3 +29%
18	++ +		1.18 1.12 -5%	32.1 25.7 -20%	2.04 1.99 -2%	22.0 32.0 +45%	1.62 1.46 -10%	2.66 2.36 -11%	74.1 45.4 -39%	3970 5145 +30%	43.2 83.0 +92%
82	++ o	184 57 -69%	0.94 2.52 +168%	32.2 36.1 +12%	1.25 1.49 +19%	11.2 38.3 +245%	1.65 2.45 +49%	2.77 2.95 +7%	148.0 63.5 -57%	2005 3305 +65%	17.9 42.9 +140%
23	+ o		0.86 1.29 +50%	13.5 11.1 -18%	3.99 5.48 +37%	26.6 45.0 +69%	1.55 1.62 +4%	2.46 3.11 +26%	57.9 34.4 -41%		
50	+ o	275 64 -77%	1.37 2.30 +68%	46.1 21.9 -52%	2.24 1.99 -11%	19.0 23.0 +41%	2.69 2.16 -20%	2.69 2.16 -20%		4570 4090 -10%	38.1 47.0 +23%
138	+ o		0.80 0.99 +24%	48.0 34.7 -28%	1.93 2.07 +7%	21.4 28.8 +35%		2.45 3.16 +29%			
			+68%	-19%	+22%	+53%	+4%	+7%	-50%	+33%	+64%

TABLE III

Data of four cases chosen from the 15 cases in the severe congestive failure group, to illustrate the wide variation in individual functions of the circulation and to emphasize that one must take into consideration all of the functions and not one or two individual ones in order to determine the true state of the circulation

Case No	V P	V C	A T	F	S V
161	203	0 37	13 5	3 20	33 0
84		0 50	41 5	1 32	14 0
182	210	0 92	47 7	1 07	11 3
90		1 54	27 0	1 88	20 0

of blood in the heart, lungs and great vessels are greater than the changes in total blood volume, indicating in this fact alone, a tendency for the blood to accumulate in the thorax and abdomen. The increase after compensation becomes reestablished indicates that there must be liberated into the blood stream considerable quantities of blood previously stagnant and out of circulation. It follows also that the term "volume clearance index" indicates the number of heart beats required to clear the heart and lungs of *actively circulating* blood.

One other feature should be emphasized. It is an important fact that when compensation becomes reestablished after congestive failure has once developed, certain of the functions of the circulation do not return to normal, notably the velocity of blood flow and the cardiac output. It may be stated in another fashion, that once heart failure has developed, the heart may never be the same again.

SUMMARY

1 Using the dye injection method, the various functions of the circulation were studied in cases of hypertension before congestive failure had developed, when congestion had appeared and when compensation had become reestablished.

2 The changes in venous pressure, vital capacity, appearance time (velocity of blood flow), cardiac output, stroke volume, volume of actively circulating blood in the heart, lungs and great vessels, total blood volume, volume clearance index (the number of heart beats required to clear the heart, lungs and great vessels of actively circulating blood), work and work per beat are reported and discussed.

3 The relative effects of rest alone and of rest plus digitalis are reported.

4 Emphasis is laid upon the fact that even in severe heart failure certain of the functions, as the flow, for example, may be within normal limits, and that only by a study of the interrelationships of all of the functions concerned can a true picture of the cardiac hemodynamics be obtained.

BIBLIOGRAPHY

- 1 HAMILTON, W F, MOORE, J W, KINSMAN, J M, and SPURLING, R G. Simultaneous determination of pulmonary and systemic circulation times in man, and of a figure related to cardiac output, *Am Jr Physiol*, 1928, **LXXXIV**, 338-344.

- KINSMAN, J M, MOORE, J W, and HAMILTON, W F Studies on circulation I Injection method, physical and mathematical considerations, *Am Jr Physiol*, 1929, *lxxix*, 322-330
- MOORE, J W, KINSMAN, J M, HAMILTON, W F, and SPURLING, R G Studies on circulation II Cardiac output determinations, comparison of injection method with direct Fick procedure, *Am Jr Physiol*, 1929, *lxxix*, 331-339
- MOORE, J W, HAMILTON, W F, KINSMAN, J M, and SPURLING, R G Studies on circulation III Description of injection method of studying circulation, with some clinical applications, *Southern Med Jr*, 1930, *xlvi*, 1131-1135
- HAMILTON, W F, MOORE, J W, KINSMAN, J M, and SPURLING, R G Studies on circulation IV Further analysis of injection method, and of changes in hemodynamics under physiological and pathological conditions, *Am Jr Physiol*, 1932, *xcix*, 534-551
- 2 BLUMGART, H L, WEISS, S, and YENS, O C Studies on velocity of blood flow, *Jr Clin Invest*, 1927 *iv*, 1-13, 15-31
- 3 STARR, I, JR, and OTHERS Studies of heart and circulation in disease, estimations of basal cardiac output, metabolism, heart size and blood pressure in 235 subjects, *Jr Clin Invest*, 1934, *xi*, 561-592

VASCULAR DISEASE IN THE OBESE DIABETIC, AND IN NON-DIABETICS; A DISCUSSION OF ARTERIOSCLEROSIS AS A CAUSE OF DIABETES

By EDGAR C BECK, M D , JAMES G FOWLER, M D , EDWARD C KOENIG, M D , F A C P , and BYRON D BOWEN, M D , F A C P ,
Buffalo, New York

Most older diabetic patients are obese or have been so. Their pathological state is, therefore, essentially that of obesity with superimposed diabetes. The association of vascular disease and diabetes in this group is far too frequent to be ascribed to coincidence alone. Those^{1, 2, 3, 4} who believe that diabetes hastens the approach and accelerates the development of arteriosclerosis refer to atheromatous lesions of the elastic and muscular arteries. The demonstration of calcium roentgenologically in the peripheral vessels has been used to detect this type of lesion, though it is realized that extensive atheromatosis may be present with minimal or even with no calcification. Such deposits occur in the deeper layers of the intima and in the media. There is some question whether sclerosis of the Monckeberg type is related to or may be part of atherosclerosis,⁵ as originally thought by Marchand. There is no essential difference, pathologically, between the sclerosis that occurs in the older diabetic and senile atherosclerosis. In analyzing the pathological descriptions of the arteries of legs amputated for gangrene at the Buffalo General Hospital, it was found that they were similar in both the diabetic and senile types. The senile group, however, was about 10 years older than the diabetic. There was close correspondence between calcium demonstrated roentgenologically and histologically. Such calcification is found more regularly in men, both diabetic and non-diabetic. Its presence increases the probability of occlusion, as has been shown by Lansbury and Brown,⁶ although extensive calcification may be present for a long period with open arteries.

It is assumed that those who have suggested that diabetes in older people may be caused by arteriosclerosis of the pancreatic vessels, which in turn produce hyalinization and fibrosis of the islands, refer mostly to arteriolar lesions. These are not necessarily associated with calcification and lipid deposits in the larger vessels, but are more intimately related to high blood pressure. These two types of sclerosis may be and commonly are found together, particularly in older people with hypertension.

The histological demonstration in diabetic patients of sclerosis of the small pancreatic arteries and arterioles, or even atherosclerosis of the larger ones, does not permit one to assume that these lesions were present at the

* Read at the Philadelphia meeting of the American College of Physicians, May 3, 1935.
From the Buffalo General Hospital and the Department of Medicine, School of Medicine, the University of Buffalo.

time the patient developed diabetes, which usually is many years before death. In fact, it is often impossible to estimate the time of onset of diabetes in an elderly patient. If it could be shown that vascular disease was more frequent in the early diabetic than in the non-diabetic, this would constitute additional evidence that the pancreatic vessels had a greater chance of being involved. In this study only obese subjects were used because of the predominance of obesity in the older diabetic, and also so that the factor

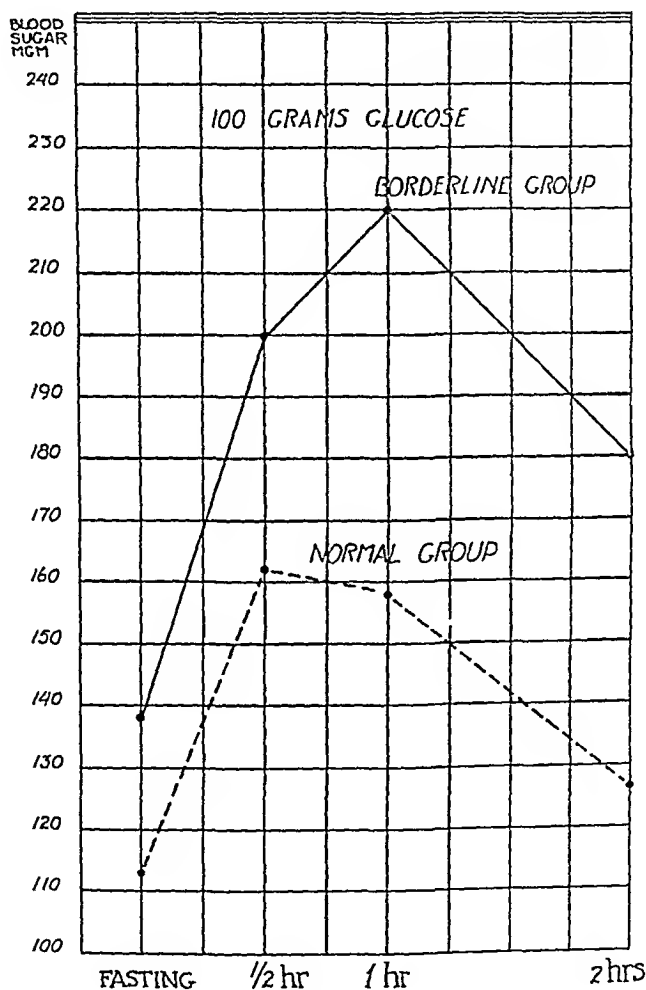


CHART I Composite Tolerance Curves

of body weight, which is so important in vascular disease in older people, should be adequately controlled. Previous studies, we believe, have not taken this factor sufficiently into account.

The patients were observed almost entirely in the Out-Patient Department. They were generally without symptoms, except those attributable to obesity. None of the diabetics required insulin. Calcification of the arteries of the lower extremities was searched for roentgenologically, their

blood pressures were followed, and their retinal arteries were studied by the ophthalmologist (J G F). The heart was not considered, because previous workers^{7,8} have shown that obese patients as a rule have large hearts and that frequently changes in the electrocardiogram are present. The patients were divided into three groups according to their glucose tolerance. The test used was 100 grams of glucose administered by mouth, subsequent to the taking of a fasting blood sugar, and absorptive blood sugar determinations taken at one-half hour, one hour, and two hour intervals⁴. In the diabetics this was not done because the diagnosis was evident. There were 49 patients, with an average age of 39 years, in the group with normal glucose tolerance. Three of these were men. Seventeen women, with an average age of 43 years, comprised the group with borderline reactions to glucose. Thirty patients, five of whom were men, made up the diabetic group. We were reasonably certain that none of this group had been diabetic for over three years. Most of them had been under active treatment.

Extreme calcification of the leg arteries was found in only two patients, both men, a diabetic 67 years old and a non-diabetic 75 years old. Traces of calcification in only the dorsalis pedis arteries occurred in two of the diabetic women. The other patients in all groups had no discernible arterial shadows.

Patients were regarded as having hypertension if the blood pressure exceeded 150 mm of mercury systolic or 100 mm diastolic, or both. According to this definition it was present in 50 per cent of the diabetic group, 43 per cent of the borderline group, and 31 per cent of those with normal glucose tolerance. These were further separated into those who had well established hypertension and those whose blood pressure was only slightly above the borderline, for the reason that a slightly elevated blood pressure is common in obese people and that it so frequently drops with the reduction of body weight. The incidence of well established hypertension occurred about equally in the normal and diabetic groups, the incidence being 18 and 20 per cent respectively. The borderline group, a much smaller one, showed an incidence of 31 per cent. The average age of those who had such hypertension was the same in each group, 49 years.

The following criteria for the presence of retinal arteriosclerosis were used: contraction of the lumen, venous compression at the arteriovenous crossings, translucency and visibility of arterial wall, the light reflex stripe of the arteries, tortuosity of arteries and capillaries, and sclerosis of choroidal blood vessels (tesselated fundi and colloid excrescences)^{9, 10, 11, 12}.

A fundus was pronounced completely negative if none of these signs were present, suggestive (\pm), when tortuosity, reduced translucency, and disturbances of the reflex stripe occurred together, definite ($1+$), when thinning of the arteries, uneven caliber and compression of the veins oc-

* Blood sugar method Meyer-Benedict technic

curred singly, or together, or in combination with the above mentioned signs. When these changes were more extreme, a 2+ designation was used, and when they were observed in combination with retinal degenerative changes, such as hemorrhages or exudates, the symbol 3+ was employed.

Retinal arteriosclerosis of all grades was found in 36.6 per cent of the diabetic group, 41 per cent of the borderline group, and in 32.6 per cent of those having normal glucose tolerance. The average age of the patients having retinal arteriosclerosis was 53, 50.5, and 50.6 years, respectively. The percentage of patients with hypertension, who also had evidence of retinal arteriosclerosis, was about the same in the diabetic and borderline groups, 72.7 and 71 per cent, while that in the normal group fell to 44 per cent. This is possibly because the patients in the normal group who had hypertension were younger than those in the other groups. The average

TABLE I
Summary of Data

	Diabetic	Borderline	Normal
Number of Cases	30	17	49
Average Age	50	43	39
Percentage Weight Above Ideal	45.8	65	66
Percentage with Hypertension	50	43	30.6
Average Age with Hypertension	53	51.6	46
Percentage with Well Established Hypertension	20	31	18
Average Age with Well Established Hypertension	49.6	49	49
Percentage with Retinal Arteriosclerosis (All Grades)	36.6	41	32.6
Average Age with Retinal Arteriosclerosis	53	50.5	50.6
Percentage of Hypertension with Retinal Arteriosclerosis	72.7	71	44
Average Age with Hypertension and Retinal Arteriosclerosis	55.6	51.6	49

TABLE II
Grades of Retinal Arteriosclerosis

Group	Average Age	±	+	++	+++	Percentage (+ or more)
Diabetic (30 cases)	50	4	2	2	1	17
Borderline glucose tolerance (17 cases)	43	2	3	2		
Normal glucose tolerance (49 cases)	39	2	9	4	1	30
						28.6

ages of patients with both hypertension and retinal arteriosclerosis were 55.6, 51.6, and 49 years, respectively. The percentage of patients in all groups who had 2+ or 3+ retinal arteriosclerosis was the same, 10 per cent, hypertension was present in all but one of these cases. Only two patients had a 3+ retinal arteriosclerosis: one, a diabetic 60 years old, hypertension, and the other a 54 year old woman with mild hypertension and normal glucose tolerance.

With the tests used, slightly less than half of our obese subjects, diabetic and non-diabetic, had no evidence of vascular disease. Were it possible to calculate the influence of the age difference which exists in the three groups, it seems probable that the incidence of vascular disease would be about the same in each group. Also in obese subjects there appears to be no striking correlation between glucose tolerance, hypertension, or retinal arteriosclerosis.

DISCUSSION

Vascular disease is common in obese people, and it is a frequent cause of death in such subjects. Hartman and Ghrist¹³ analyzed the blood pressures of 2042 consecutive patients, males and females about equally divided. They found the blood pressures of the overweight group to be about 12 per cent higher than those in the underweight. Dublin¹⁴ has shown by a medical-actuarial investigation that the death rate from arterial disease was decidedly increased in individuals who were overweight, especially after 45 years. At that age the death rate for those of normal weight was 45 per 100,000, but for those whose weight was 15 to 24 per cent increased, the death rate was 97. Preble¹⁵ in his study of 1000 patients with obesity found the average blood pressure of those after the age of 40 to be 160 systolic and 100 diastolic. Fifty-three of 700 of these patients had glycosuria, the greater number of them being in the fifth decade. Master and Oppenheimer⁷ found hypertension (blood pressure 150 mm systolic, or more) in 67 per cent of 97 patients with obesity. Their ages varied from 10 to 58 years, but nearly all of them were between 35 and 50. Smith and Willis⁸ made a post-mortem study of 136 obese patients, who were more than 13 per cent overweight and whose average age was 52.1 years. Only four had diabetes. We judge that many of the deaths were postoperative. Forty-five per cent had had "well marked hypertension." Of these the average blood pressure had been 175 systolic and 82 diastolic. These figures attest the high incidence of vascular disturbances in obesity. If it could be shown that obese diabetics had a higher blood pressure than obese non-diabetics, then hypertension might be held a contributory factor to diabetes in such cases. Also, if hypertension with arteriosclerosis in itself were a cause of diabetes, then it would be expected that more patients with hypertension, even those without obesity, would develop clinical diabetes. A survey of several textbooks and clinical studies of large series of cases of hypertension did not give any information on this point. Certainly it is not our clinical impression that diabetes is an important sequel of hypertension. It is well known that extreme arteriolar sclerosis of the pancreatic vessels is common in patients with so-called malignant hypertension or sclerosis, yet, clinical diabetes in such patients appears to be uncommon.

Patients with hypertension frequently have slight glycosuria, high renal thresholds for sugar, and a distortion of the so-called normal curve after the ingestion of glucose. Different observers vary widely in their findings

and opinions on this point, as John¹⁶ has brought to our attention. He found in a study of the glucose tolerance of 50 of his own patients with hypertension that the number of "diabetic curves" increased with age. This would suggest that hypertension produced an increasing insufficiency of insulin. Rømkke,¹⁷ however, made similar observations, but also showed that the absorptive blood sugar curve was much the same in older people whose blood pressures were normal. Marshall¹⁸ likewise found distinct and prolonged hyperglycemia in 50 per cent of healthy old people after the ingestion of glucose. Many terms have been given to such distorted curves. "Potential diabetes" or "pre-diabetes" are common. Schmidt¹⁹ proposed "sthenischen Diabetes" and Kylan¹⁹ "hypertonie Diabetes". There is insufficient proof that patients who have abnormal curves develop clinical diabetes with enough regularity to justify the word "diabetes" in the nomenclature. The various factors, which affect the inflow and outflow of glucose in the blood stream, are involved and complicated. We believe that such a test cannot safely be considered specific for clinical diabetes unless fasting hyperglycemia is present and then only under certain conditions. The patient should previously have been eating an unrestricted diet. Also, there should be freedom from hyperthyroidism, fever, and nitrogen retention.

In 1894 Hoppe-Seyler²⁰ reported the autopsy findings in a case of diabetes in which he believed the islet changes were caused by arteriosclerosis. In 1904 he²¹ added nine such cases. Upon examination of his material, it was found that all of his patients had generalized arteriosclerosis and that the majority were in the seventh decade, three had gangrene of a lower extremity. He also examined the pancreatic vessels of a larger group of non-diabetics of the same age. He found that the diabetics had a higher grade of sclerosis of the pancreatic vessels and that in them pancreatic cirrhosis was more extensive. It was his idea that the changes in the islands were entirely secondary to the vascular changes.

Similarly, Herxheimer²² contends that arteriosclerosis is a prominent primary factor in the production of diabetes in older people. He has drawn the analogy between nephrocirrhosis produced by arteriosclerosis and pancreatic cirrhosis.

Pathologists generally agree that sclerosis of the pancreatic vessels is a common finding in older patients. Barron²³ concludes that pancreatic atherosclerosis is frequently encountered and that it is a probable cause of diabetes. Cecil²⁴ found that most middle aged patients had some degree of such sclerosis and expressed the opinion that hyalinization and fibrosis of the islands were produced in a manner similar to such changes in the glomeruli.

Kraus²⁵ after a study of the structural changes in all of the endocrine glands in diabetics concluded that all diabetes was pancreatogenic, but he believed that there was, in spite of the great variability of the findings, a

contrast between the pancreas of the young and older diabetic. The pancreas was smaller in the young, atrophy or hydropic degeneration of the islands—the elective island disease of Weichselbaum—was commonly seen. In the older patient the pancreas showed inter- and intra-acinous connective tissue proliferation, cirrhosis, lipomatosis, and atrophy of the tubules. The changes in the islands were predominantly hyaline. A majority of the older patients showed sclerosis of the pancreatic arteries. He encountered some pancreases of older patients in which the changes commonly found in youthful patients were present, and vice versa.

Warren²⁶ studied 259 pancreases of diabetic patients. He thought the islands normal, as far as could be determined histologically, in 27 per cent. No definite correlation between island lesions and intra-acinar fibrosis could be determined. Fifteen of the 259 showed marked sclerosis of the pancreatic vessels. He comments that the splenic artery, which is on the same circuit as the pancreaticoduodenal artery, often shows extreme sclerosis, while the arteries of the pancreas may be relatively free. He believes that from a pathological viewpoint arteriosclerosis is not an outstanding cause of changes in the islands.

Peterson²⁷ considered the subject of diabetes and arteriosclerosis pathologically. He found some degree of sclerosis of the arteries and arterioles of the pancreas in nearly every case. He states, "It appears that disease of the arteries and arterioles is much more advanced in diabetics than in non-diabetics of the same age. It may be inferred that diabetes hastens the development of the arterial disease. It may be contended that arterial changes come first and cause diabetes, but the degree of involvement in many instances seems hardly sufficient to cause such a damage to the pancreas, and, also, sclerosis of the pancreatic vessels is not always associated with diabetes. I am inclined, therefore, to adopt the view that diabetes hastens the development of arteriosclerosis in some way."

It appears then that some authors, when speaking of sclerosis of the pancreatic arteries, refer to the larger vessels, while others refer to the smaller. The recent work of Rosenthal²⁸ leads one to suspect that atherosclerosis and arteriolar sclerosis are, possibly, in some way related. He considered this subject critically from clinical and postmortem material and concludes that hypertension plays an important role in the development of atherosclerosis, but he believes that there are etiological factors other than hypertension, since 48 per cent of his cases of atherosclerosis did not have hypertension. Pathologists agree that atherosclerosis of the larger arteries is not a common finding in early hypertension.

All three clinical states under consideration, obesity, hypertension, and diabetes, appear to be unquestionably influenced by an hereditary factor. All three may be found together, or in various combinations. It appears clear that obesity increases the likelihood of both diabetes and hypertension, but less certain that the presence of hypertension contributes to the proba-

bility of diabetes, since the incidence of hypertension is about the same in the non-diabetic obese person as in the obese diabetic

With the mechanism of the production of diabetes so incompletely understood, its pathologic anatomy so variable, and, also, the possibility of extra-pancreatic influences so definite, it is not surprising that many should regard the inception of diabetes as a functional disturbance. One finds it difficult to believe the cause as being one thing in youth and as belonging to the degenerative diseases after the age of 40, as Enklewitz²⁹ has recently propounded. Perhaps it is more logical to think of it as a different reaction at various ages. It is conceivable, also, that the presence of vascular degenerative changes in the pancreas may be a factor in the production of diabetes, but it seems unlikely that it is the sole cause. If it were so, diabetes in the aged and in patients with high grade hypertension should be more common, unless an elective vascular disease of the pancreas exists. Also, atherosclerosis in older people is more common in men than in women. Diabetes, however, in the same age group is more common in women.

SUMMARY

Calcification of the arteries of the lower extremities (demonstrated roentgenologically), which is so common, particularly in the older, uncontrolled diabetic, is essentially absent in early diabetics and in obese people, some of whom are potential diabetics.

No evidence was found to show that hypertension or retinal arteriosclerosis could be correlated with the obese patients' ability to use glucose. The incidence of hypertension appears to be higher in older diabetics. We believe, however, that this is essentially related to obesity and not to diabetes.

The proposal that diabetes in older people is commonly caused by sclerosis of the pancreatic blood vessels is discussed. Direct proof that sclerosis of the pancreatic vessels causes diabetes cannot be determined by clinical methods, nor can it be held responsible as a primary cause of diabetes when found at necropsy. Nevertheless, it seems improbable that such sclerosis can be regarded as a general cause for diabetes in older people.

BIBLIOGRAPHY

- 1 BOWEN, B. D., KOENIG, E. C., and VIELE, A. A study of the lower extremities in diabetes as compared with non-diabetic states, from the standpoint of x-ray findings, with particular reference to the relationship of arteriosclerosis and diabetes, *Bull. Buffalo Gen. Hosp.*, 1924, 11, 35-41.
- 2 JOSLIN, E. P. Arteriosclerosis and diabetes, *Ann. Clin. Med.*, 1927, 1, 1061-1080.
- 3 BOWEN, B. D., and KOENIG, E. C. Arteriosclerosis and diabetes, including a roentgenological study of the lower extremities, *Bull. Buffalo Gen. Hosp.*, 1927, 1, 31-43.
- 4 SHEPARDSON, H. C. Arteriosclerosis in the young diabetic patient, *Arch. Int. Med.*, 1930, 14, 674-689.
- 5 ASCHOFF, L. Introduction to "arteriosclerosis," E. V. Cowdry, 1933, Macmillan Co., New York, page 6.

- 6 LANSBURY, J, and BROWN, G E Clinical significance of calcification of arteries of lower extremities, *Proc Staff Meet, Mayo Clin*, 1934, 1, 49-55
- 7 MASTER, A M, and OPPENHEIMER, E T Study of obesity Circulatory, roentgen-ray and electrocardiographic investigations, *Jr Am Med Assoc*, 1929, xcii, 1652-1656
- 8 SMITH, H L, and WILLIUS, F A Adiposity of heart clinical and pathologic study of 136 obese patients, *Arch Int Med*, 1933, lxi, 911-931
- 9 PINES, N Arterial hypertension and retinal changes, *Brit Jr Ophth*, 1927, xi, 489-522
- 10 FRIEDENWALD, H Pathologic changes in retinal blood vessels in arteriosclerosis and hypertension, *Trans Oxford Ophth Congr*, 1930, 1, 452-530
- 11 MOORE, R F Medical ophthalmology, 1922, P Blakiston's Son and Co, Philadelphia
- 12 FISHLER, A M, and OPPENHEIMER, B S Differentiation and significance of certain ophthalmologic pictures in hypertensive diseases, *Arch Int Med*, 1930, xli, 901-920
- 13 HARTMAN, H R, and GURIST, D G Blood pressure and weight, *Arch Int Med*, 1929, xlv, 877-881
- 14 DUBIN, L I Influence of weight on certain causes of death, *Human Biol*, 1931, 130 (Cited from SYDNSTRICKER, E Arteriosclerosis, E V Cowdry, 1933, Macmillan Co, New York, page 134)
- 15 PRUITT, W E Obesity observations on one thousand cases, *Boston Med and Surg Jr*, 1923, clxxviii, 617-621
- 16 JOHN, H J Hypertension and diabetes *Ann Int Med*, 1932, 1, 1462-1486
- 17 RÖMCKI, O Der Blutzucker im alteren Alter, insbesondere bei hypertensiven Zuständen Zur Frage der chronischen Hyperglycämien mit normaler alimentärer Reaction, *Acta med Scandiv*, 1931, Supp xxxv, 1-150
- 18 MARSHALL, F W Sugar content of blood in elderly people, *Quart Jr Med*, 1930-31, xxiv, 257-284
- 19 SCHMIDT, and KYLIN (Cited by Romeke¹⁷)
- 20 HOPFF-SYLLER, G Beitrag zur Kenntnis der Beziehungen der Erkrankung des Pankreas und seiner Gefasse zum Diabetes mellitus, *Deutsch Arch f klin Med*, 1894, lii, 171-177
- 21 HOPFF-SYLLER, G Über chronische Veränderungen des Pankreas bei Arteriosklerose und ihre Beziehung zum Diabetes mellitus, *Deutsch Arch f klin Med*, 1904, lxxxi, 119-162
- 22 HERNHOFER, G Zur Frage der Arteriosklerose, *Centralbl f allg Path u path Anat*, 1923, xxxiii, 111-126
- 23 BARRON, M Diseases of pancreas, *Arch Int Med*, 1925, xxxv, 807-817
- 24 CECIL, R L Discussion of SHEPARDSON, H C¹
- 25 KRAUS, E J Die pathologisch-anatomischen Veränderungen des Pankreas beim Diabetes mellitus, *Handbuch der speziellen pathologischen Anatomie und Histologie*, 1929, 622-747
- 26 WARREN, S Pathology of diabetes mellitus, 1930, Lea and Febiger, Philadelphia, page 58
- 27 PETERSON, R F The relation of hypertension and arteriosclerosis to diabetes mellitus A thesis submitted to the faculty of the Graduate School, the University of Minnesota, 1927
- 28 ROSENTHAL, S R Studies in atherosclerosis chemical, experimental and morphologic III and IV Roles of cholesterol metabolism, blood pressure and structure of aorta, fat angle of aorta (F A A), and infiltration-expression theory of lipid deposit, *Arch Path*, 1934, xviii, 473, 660-698
- 29 ENKLEWITZ, M Diabetes and coronary thrombosis, *Am Heart Jr*, 1934, 1, 386-395

STUDIES RELATING VITAMIN C DEFICIENCY TO RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS; EXPERIMENTAL, CLINICAL AND GENERAL CONSIDERATIONS ~

II RHEUMATOID (ATROPHIC) ARTHRITIS

By JAMES F RINEHART, M D , *San Francisco, California*

A border-land between rheumatic fever and rheumatoid arthritis has long been recognized. Particularly in young adults clinical distinction may prove difficult or one may find an apparently typical rheumatic fever with carditis progress into a characteristic rheumatoid arthritis. Klinge and Gizmek¹ find that although acute and subacute rheumatic fever and chronic polyarthritis are usually easily differentiated, both disease pictures are so closely bound together in the arthritic and general pathology that a "rheumatic" basis may be assigned to both. Dawson² has lent further support to the concept of a relationship of the two diseases in showing that the early pathological change found in the subcutaneous nodules of rheumatic fever and rheumatoid arthritis, are essentially identical. This evidence, together with encouraging early observations made on the joints in scurvy^{3,4} led to a rather extensive study of the scorbutic arthropathy. It is the purpose of this paper to report the findings of this study and to draw attention to a rather convincing amount of data suggesting that vitamin C under-nutrition may be an etiological factor in at least some of the cases classified as rheumatoid arthritis.

EXPERIMENTAL METHODS

The methods employed consisted briefly in maintaining guinea pigs for rather prolonged periods of time on a basic vitamin C free diet,† supplemented with inadequate amounts of vitamin C. To study the influence of infection, parts of each experimental series were infected. Control groups

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935

This work has been made possible by research funds granted from the Christine Breon Fund for Medical Research

The first part of Dr. Rinehart's article appeared in the preceding number of the ANNALS

† The basic diet used is as follows

	Per cent
Ground rolled oats and bran—equal parts by volume	56
Powdered skimmed milk (baked at 110° for 2 hours)	30
Butter fat	10
Sodium chloride	0.5
Osborne-Mendel salt mixture	10
Dried yeast	15
Cod-liver oil (standardized)	10

Care is used in securing a thorough mixture of the above ingredients. Guinea pigs eat this diet well and, with adequate vitamin C supplement, grow and thrive

of course, were maintained on the basic diet adequately supplemented with vitamin C and subjected to the same infection. The material of this study comprises 12 series of experiments. Inasmuch as pathological observations are in essential agreement in the various experiments, no attempt will be made to report individual experiments. Sufficient detail will be found in the appended protocols, to guide anyone interested in repeating the experimental work. No sharp line can be drawn between the experiments pertaining to rheumatic fever and to the chronic arthritis. An over-lapping occurs here as is observed clinically.

THE ARTHRITIS OF SUBACUTE OR CHRONIC SCURVY

One of the first objective manifestations of vitamin C deficiency in the guinea pig is an arthropathy which is characterized by pain, swelling and limitation of movement in multiple joints. The joints exhibiting the most obvious involvement, and the usual, though not invariable sequence, are



FIG. 1 Diffuse fusiform swelling of the wrists, an early manifestation of vitamin C deficiency in the guinea pig

knees, wrists, and elbows. These have been most carefully studied, but it is probable that no joints are immune. Figure 1 illustrates a characteristic appearance of an early arthritic change with a fusiform swelling about the wrists.

THE EARLY CHANGES IN SCORBUTIC ARTHROPATHY

An exhaustive study has not been made of the earliest changes in the scorbutic arthritis. However, joints of several animals have been inspected shortly after the onset of stiffness and swelling. The periarticular tissues are seen to show an edematous, hemorrhagic appearance. Microscopically, red blood cells and serum are found, spreading apart connective tissue cells, and frequently, relatively broad hyaline streaks of a peculiarly packed fibrin are seen. At this time or shortly later, the connective tissue cells begin actively to proliferate, the hemorrhagic appearance subsides and we see an imperfectly vascularized and frequently edematous granulation tissue thickening the capsule and obscuring the underlying tendons and bony prominences.

THE ARTHROPATHY OF SUBACUTE OR CHRONIC SCURVY

A much more extensive material has been studied in the later stages of the scorbutic joint disability. For convenience and clarity, it is best to consider separately the changes in the various anatomical structures forming and surrounding the joint.

Synovial Proliferation and Pannus Formation A proliferative reaction of the synovial membrane is an almost constant finding. Usually associated with the synovial proliferation and frequently merging with the proliferating cells is a hyaline "fibrinoid" material. Figure 2 illustrates a typical reaction of this type. No sharp distinctions can be drawn between cells clearly recognizable as synovial and less differentiated connective tissue cells which, intermingled with the fibrinous material, extend from joint recesses as long tongue-like processes into the joint cavity and over the articular surfaces. Figure 3 shows the detail of such a fibrous and "fibrinoid" pannus.

Subsynovial and Peritendinous Lesions The connective tissue beneath the synovial membrane and that about the tendons inserting around the joint present analogous changes. Here again, small extravasations of blood, streaks of fibrin and a reactive hyperplasia of connective tissue cells contribute further to the swelling deformity and limitation of movement in the joint.

Articular Cartilage In addition to diffuse thinning, a retrogressive change, apparently a de-differentiation of areas of the articular cartilage, is not uncommonly seen. In places the surface of the articular cartilage is replaced by undifferentiated and at times vascularized connective tissue. The pannus described is, in some instances, adherent to the articular surfaces. The retrogressive change at the surface of the articular cartilage and apparent "perichondral" proliferation are shown in figure 4.

Rarefaction of Bone Thinning of bone trabeculae is characteristic of chronic vitamin C deficiency. This rarefaction of bone involves apparently the entire skeleton but is most prominent at the bone ends. The change is

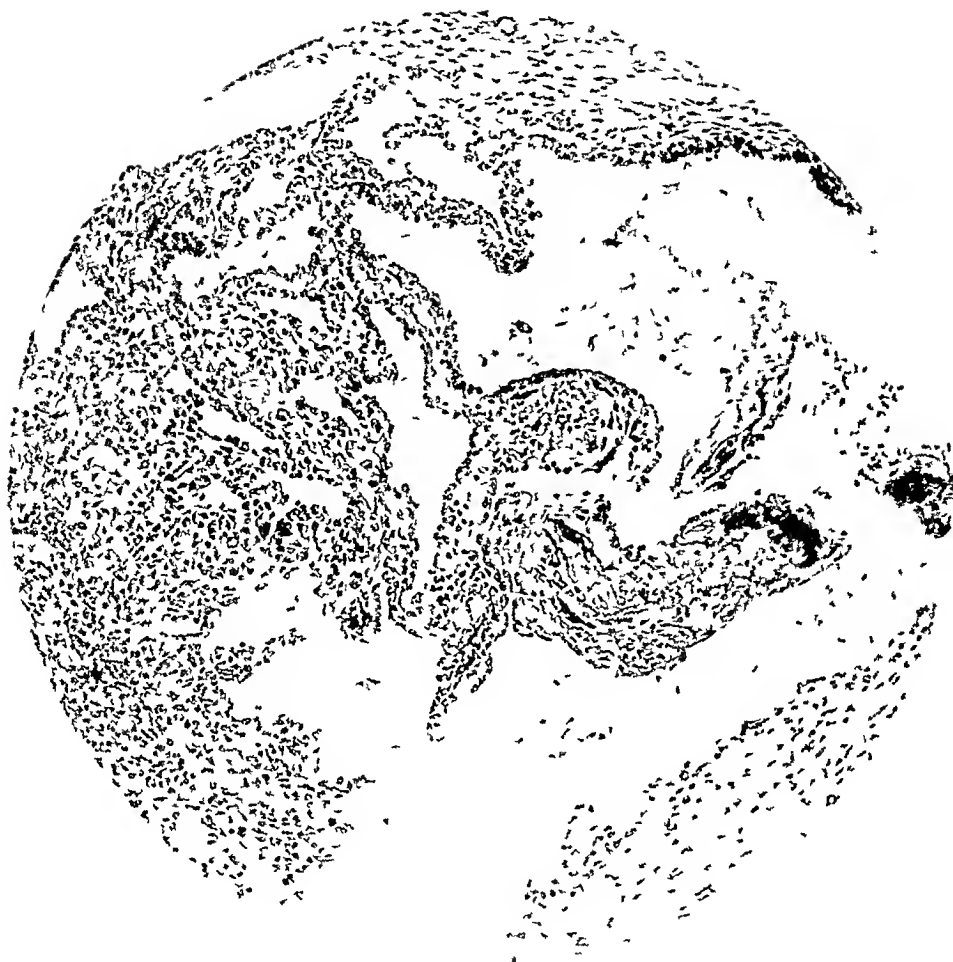


FIG. 2 A moderately intense proliferation of the synovial membrane from a recess in the knee joint of a guinea pig subjected to a subacute vitamin C deficiency and infection (beta streptococcus) $\times 200$

clearly evident in microscopic sections (figure 5), and has been repeatedly demonstrated by roentgen-ray examination. Figure 6 illustrates this change.

Muscle Some degree of muscle atrophy and degeneration is also a characteristic effect of prolonged vitamin C deficiency. An interstitial edema of the muscle is frequently seen to contribute to the periarticular swelling. In some of the more severe deficient states, hemorrhagic stippling of the muscle may occur. Some degree of muscle atrophy or degeneration is almost regularly found. Occasionally a widespread muscle degeneration dominates the pathologic picture. It would appear that this occasional severe myopathy is an effect of capillary hemorrhage and consequent cellular anoxemia.



FIG 3 Fibrous and "fibrinoid" pannus extending from a joint recess of the knee over the articular cartilage. Relatively acute scurvy and bronchopneumonia (*B. bronchisepticus*). The fibrinous material shows as grayish-black lines in microphotograph $\times 200$

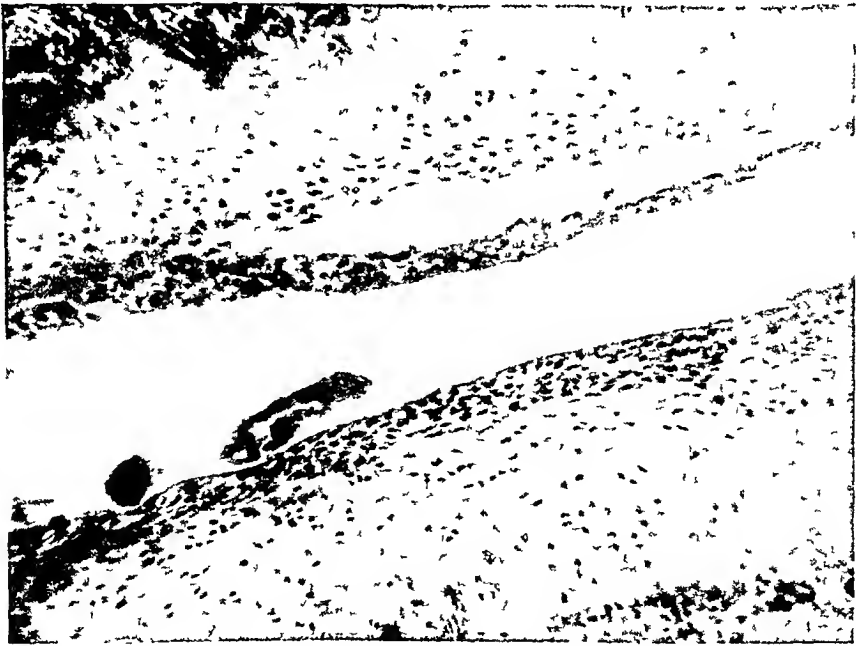


FIG 4 Showing a retrogressive change in the articular cartilage, a dedifferentiation of the surface cells at one side and an apparent perichondrial proliferation with an associated fibrinous material at the opposite surface. Subacute scurvy and infection—duration 48 days. Developed spontaneous bronchopneumonia (*B. bronchisepticus*) on the twenty-fifth day $\times 200$



FIG 5 Showing in low magnification the characteristic changes in the scorbutic arthropathy. The early pyrus extending from joint recesses is indicated by the arrows. The thinning of the bone trabeculae may be seen, and the marked capsular thickening is evident $\times 18$

Periarticular Reactions—Subcutaneous Nodules The reactions in the capsular tissues are, perhaps, of greatest interest. The early sanguinous edema has been noted. Somewhat later, the capsular connective tissue undergoes a marked proliferative reaction. Commonly, streaks of hyalinized fibrin lie in intimate association with the reactive connective tissue. The tissue, on section, often shows a striking edema. Somewhat later, a



FIG 6 This x-ray shows the hind leg of a control animal on the left, contrasted with a vitamin C deficient animal on the right. The excised limbs were exposed simultaneously, both were in an extended position. The limitation of extension is apparent in the scorbutic joint. The diminished density of the scorbutic bone, particularly at the ends about the knee joint, is clearly shown. This observation has been repeatedly verified.

gradual diminution of the periarticular thickening may occur, coincident with the shrinkage of the connective tissue. Figure 5 illustrates the topography of the intra- and periarticular lesions. A most interesting observation is the not infrequent development of discrete circumscribed fibrous

tissue nodules beneath the skin about the joints. Sometimes they are moveable beneath the skin and at other times are found more or less attached to an underlying bony prominence. The knee joint shown in figure 7 shows two such subcutaneous fibrous nodules as well as the thickening and deformity of the joint produced by scurvy. The position of the joint shows the limitation of extension. Microscopic sections of the subcutaneous nodules show an edematous, cellular, fibrous tissue, usually associated with



FIG. 7. A striking scorbutic arthropathy knee joint photographed in an extended position, showing limitation of extension, diffuse fibrous tissue thickening about the joint and two fibrous subcutaneous nodules. Uncomplicated vitamin C deficiency. Duration of experiment—70 days. Degree of deficiency, moderately severe.

irregular strands of brilliantly eosinophilic hyalinized fibrin (figure 8). The hyaline fibrin is in intimate association with connective tissue cells, and appears to correspond to the "fibrinoid" degeneration of Klinge.⁵ The experimentally produced subcutaneous nodules resemble most closely the pathologic picture of the subcutaneous nodules of rheumatic fever and the earlier nodules of rheumatoid arthritis, excellently described and illustrated by Dawson.²

THE EFFECT OF INFECTION SUPERIMPOSED ON THE CHRONIC SCURVY

The arthritic pathology described occurs in the absence of any introduced or demonstrable infection. Some infections, however, have been found to accentuate and accelerate the pathological process. This influence is clearly shown in the following experiment:

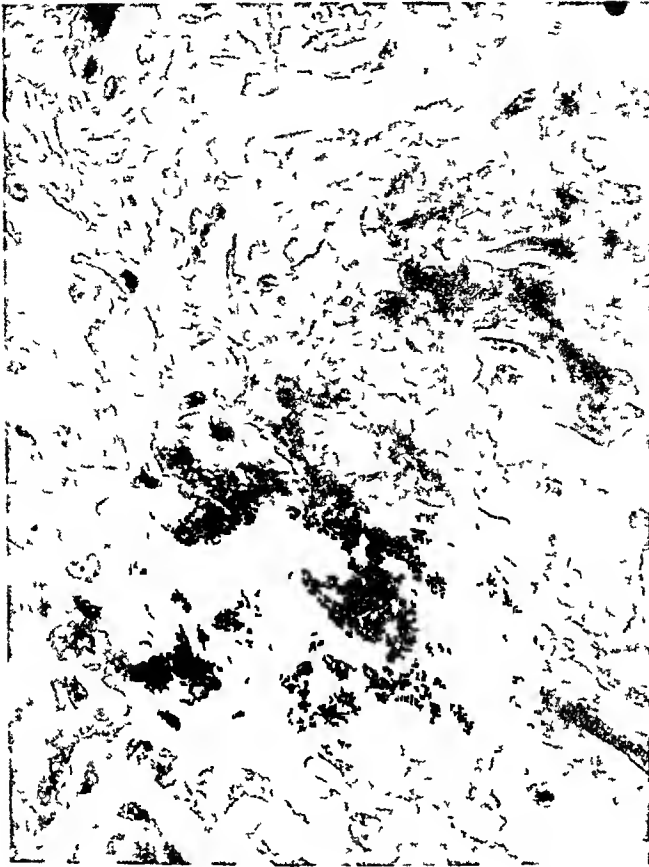


FIG 8 A portion of an experimental subcutaneous nodule developed in an animal subjected to chronic vitamin C deficiency and infection. Streaks of a brilliantly eosinophilic hyalinized fibrin together with a reactive hyperplasia of imperfectly vascularized connective tissue constitutes the structure of this lesion, and corresponds closely to the rheumatic nodule. $\times 400$

Experimental Series 14

Nov 1, 1934 A group of 13 animals were placed on the basic diet with an adequate daily supplement of orange juice (4 c c). The animals were in groups in three cages. Nov 23, 1934 One animal in a cage of five developed a spontaneous respiratory infection, which was later determined to be due to *B bronchisepticus*. Four days later, four other animals in the cage developed the same type of infection. Eight other animals in two other cages showed no evidence of infection. At this stage, five non-infected animals were placed in a larger cage with the four infected animals, and the group was transferred to a separate room. Of these animals, five were placed on a scorbutic regime, and four continued to receive 5 c c orange juice daily. Four animals were maintained unexposed to infection and subjected to the same scorbutic regime. In this instance, the scorbutic regime consisted of total deprivation of vitamin C for 18 days beginning Nov 29, then a supplement of 1 c c on alternate days for 16 days, when the experiment was concluded. The five scurvy and four control animals in the infected cage all showed evidence of pulmonary infection. The scurvy animals exposed to infection all developed frank arthritic manifestations in from 10 to 15 days with an average time of onset 13 days after the deprivation of vitamin C. The non-infected scorbutic animals in this series showed

no arthritic manifestations for periods of 24 to 32 days, with an average time of onset of 31 days. Further, the arthritic manifestations in the group exposed to both scurvy and infection were clearly more severe than those subjected to scurvy alone. The animals exposed to the infection, but given an adequate orange juice supplement, although developing infection, showed no arthritic manifestations.

It would appear quite evident that the infection, in this instance, augmented the scorbutic effect in development of the arthritic lesions. Essentially similar observations have been made with other experimental infections. In other instances, however, this has not been apparent. It would seem that the type and virulence of the infection are of importance in this relationship.¹

SUMMARY OF THE PATHOLOGICAL CHANGES IN THE SCORBUTIC ARTHIROPATHY

The arthritis of subacute or chronic scurvy, uncomplicated or with superimposed infection, is characterized within the joint by synovial proliferation and "fibrinoid" and connective tissue pannus formation. The capsular, peritendinous and intermuscular tissues show fibrin deposition, and reactive hyperplasia of an imperfectly vascularized connective tissue. These changes contribute to pain, swelling and limitation of movement or effectual ankylosis in multiple joints. Striking lesions, frequently observed, are subcutaneous nodules histologically characterized by streaks of fibrin and reactive hyperplasia of connective tissue, and bearing a close resemblance to "rheumatic" nodules. Muscle atrophy and degeneration are regularly observed in the scorbutic arthritis. A general skeletal rarefaction develops, which is most marked at the bone ends. Certain infections accelerate and intensify the arthritic process, while others do not.

REPRESENTATIVE PROTOCOLS

Series 7 No 189 Received basal diet plus adequate orange juice supplement for 15 days. 6/1/33 to 6/8/33, no orange juice. 6/8/33 to 6/20/33, 1 c.c. daily. 6/21/33 to 6/26/33, 0.5 c.c. daily. 6/27/33 to 7/16/33, 1 c.c. daily and 7/16/33 to 8/2/33, 0.5 c.c. daily. On 6/16/33 the animal was infected by inoculation of a broth culture of beta streptococcus (source spontaneous lymphadenitis of guinea pig). The inoculation was made into the skin of the left groin, and the animal developed a local skin infection and lymphadenitis. *Course* 6/24/33, the left knee is stiff with limitation of extension, four days later, the right knee also stiff. 7/21/33, both knees are stiff and swollen. 7/25/33, the elbows are also swollen. 8/2/33, animal sacrificed. *Pathological notes* General nutrition is fair. The mucous membrane of the bladder is hemorrhagic. A small abscess is present.

* A few observations suggest that vitamin C deficiency may produce in the joints a locus of diminished resistance to the actual lodgement of bacteria and so predispose to the development of a truly infectious (suppurative) arthritis. This is illustrated by an observation on a guinea pig in Experimental Series Number 12. This animal was in a group subjected to chronic vitamin C deficiency, but had exhibited swelling of joints, particularly of one knee, that was much more marked than in the other members of the series. The temperature was elevated. At autopsy, an acute suppurative arthritis was evident in the most swollen knee. Cultures of the spleen and inguinal lymph node yielded a green streptococcus.

between the liver and the diaphragm. A little hemorrhage is seen over and under the right knee. This joint shows capsular thickening, synovial proliferation and early pannus formation.

Series 8 No 201 This animal was one of a group subjected to vitamin C deficiency for a period of approximately 41 days. These animals received 1 c c of orange juice three times a week during the course of the experiment. Weight at onset of the experiment, 8/17/33, 374 grams. *Course* 9/14/33, slight thickening of the tissues about the knees first noted. 9/20/33, slight stiffness and thickening of the knees, no swelling. 9/28/33, weight, 248 grams. Knees thickened and stiff. Animal sacrificed. *Pathological notes* Moderate thickening of the capsule of the right knee. Moderate congestion and hemorrhagic stippling of the bladder mucous membrane.

Series 8 No 210 This animal was one of a group in the same experiment subjected to the same dietary regime but also to infection with a hemolytic staphylococcus. This animal as the others of the group showed a more marked arthropathy than the animals subjected to scurvy alone, even though the local reaction at the site of infection was quite mild. *Course* 9/14/33, knees stiff and slightly thickened. On this date the animal was infected by intracutaneous inoculation with a broth culture of hemolytic staphylococci into the skin of the neck. A mild non-suppurative cervical adenitis resulted. 9/20/33, the right knee is definitely swollen. 9/28/33, both knees thickened, stiff and swollen. Animal sacrificed. Some hemorrhage in chest wall. Right knee shows considerable capsular thickening composed of a brownish granulation tissue. There are areas of hemorrhage in this tissue. The muscle below the knee appears edematous and shows some recent hemorrhage.

Series 9 No 247 This animal was placed on the basal diet 10/25/33. For the first 20 days a total supplement of 8 c c of orange juice was given. At this time, 11/15/33, the animal exhibited swelling and stiffness of both knees and tenderness of the wrists. For the next two and one-half months, the animal received alternately adequate and inadequate amounts of orange juice, the average daily intake being 17 c c. Infection was introduced (beta hemolytic streptococcus) into the skin of the neck on 12/17/33. After 2/7/34, the animal received 1 c c of orange juice daily until death on 4/30/34, approximately six months after the onset of the experiment. *Course* The general nutrition of the animal remained fair, and more or less arthritic disability was present in the knees, wrists and elbows throughout the experiment, with several episodes of swelling. *Pathological notes* At autopsy, a fibrous nodule was found near the left elbow. The knee and elbow joints on section showed bone atrophy and synovial proliferation. The elbow in addition showed irregularity of the articular surface and apparent perichondrial proliferation. The subcutaneous nodule showed hyalin streaks of fibrin and reactive hyperplasia of the connective tissue.

Series 15 No 368 Animal placed upon basal diet 11/20/34, and maintained with an adequate daily supplement of orange juice (4 c c) to 12/4/34, when the supplement was entirely removed for 13 days. Then animal received orange juice 1 c c on alternate days until 1/7/35 when sacrificed. *Course* The temperature record indicated that the animal had developed a spontaneous infection about 12/14/34. Swelling of the knees was noted 12/15/34. On 12/24/34 the knees were swollen and tender, and the elbows were tender. *Pathological notes* Autopsy revealed an extensive bronchopneumonia (*B. bronchisepticus*). The costochondral junctures were moderately thickened. The capsular tissues of the right knee were distinctly thickened with a brownish-red granulation tissue. There was no evidence of fresh hemorrhage. A protruding nodule of granulation tissue was found at the inner aspect of the right elbow. Sections of the knee

showed fibrous and fibrinous pannus, buckling of the cartilage and fibrous tissue thickening of the capsule. The elbow showed a broad fibrinous and fibrous tissue pannus.

Series 15 No. 376 Same series and dietary regime as 368, without however any evidence of infection. The animal survived until sacrificed on 1/31/35. *Course* General condition and nutrition remained good. The animal first developed tenderness of knees without any swelling on 12/14/34. On 12/21/34, the knees were tender and slightly swollen, and the left wrist was swollen and tender. No elevation of temperature. On 1/31/35, the animal showed stiff, thickened and tender knees with subcutaneous nodules on both knees (see photograph in text). *Pathological notes* The left knee showed diffuse fibrous tissue thickening of the capsule, with in addition two subcutaneous nodules. The periarticular tissues were edematous and congested. The right knee showed a similar appearance. One subcutaneous nodule was present. The capsular tissue of the right knee was 1 mm. thick. The left wrist also showed periarticular thickening.

FUNDAMENTAL SIMILARITIES OF THE EXPERIMENTAL LESIONS TO THOSE OF RHEUMATOID ARTHRITIS

One familiar with the pathology of rheumatoid arthritis will at once recognize certain basic similarities of the experimental arthritis described, to this condition. The study of Nichols and Richardson,⁶ on the pathology of chronic arthritis, remains a classic. Particularly with respect to rheumatoid arthritis, relatively little has been added to their original observations. The work of Fisher⁷ has served to confirm and in some respects extend their observations. The essential changes can be no more clearly or succinctly given than in the words of Nichols and Richardson, who in referring to proliferative arthritis (rheumatoid) say "In this type of joint lesion the primary change occurs as a proliferation of the synovial membrane and the perichondrium of the articular cavity, combined in many cases with a synchronous proliferation of the connective tissue and the endosteum of the epiphyseal marrow directly below the joint cartilage", and further "The proliferation and extension over the surface of the cartilage of the synovial membrane is the earliest and most marked feature of these joints. The pannus may be composed of a very vascular granulation tissue infiltrated with lymphoid and plasma cells, with comparatively little intercellular material or may be a very dense fibrous tissue with very few vessels and no obvious infiltration." Of the periarticular and capsular tissues they state "In all cases of proliferative arthritis changes occur in the capsule, usually synchronous with changes in the synovial membrane. This change consists in a proliferation of the connective tissue of the capsule and leads to a greater or less thickening usually of the entire capsule." They note that in the early stages, there may be a connective tissue with little intercellular substance which later becomes denser with more or less hyalinization and vascular obliteration. In both stages the tissue may or may not be infiltrated with lymphoid and plasma cells. Fisher's observations are in essential agreement. In addition, he notes that in the more central parts of the articular cartilage one may often find shallow ulcers whose floor is formed by connective tissue

formed by metaplasia of the superficial cartilage cells. In the later stages of the disease the extreme fragility of the affected bones is noted. Llewellyn and Jones⁸ have suggested substitution of the term fibrositis for chronic rheumatism, because they consider the basic anatomic lesion is one of inflammatory overgrowth, or hyperplasia of the white fibrous connective tissue. They further point out that, in chronic articular rheumatism, the periarticular, subsynovial and ligamentous tissues are at times more often and more deeply affected by the morbid process than the synovial or bony elements. Emphasis is also placed upon the importance of muscular degenerations in the rheumatic syndrome. Klinge and Grzimek's¹ studies indicate the importance of the "fibrinoid" degeneration in this type of arthritis as well as in rheumatic fever. The essential identity of the anatomic lesion in the experimentally produced subcutaneous nodules and those of rheumatic fever and rheumatoid arthritis has been noted. Considerable significance is attached to the experimental occurrence of this lesion because of its unusual character. Many observers have stressed the bone atrophy accompanying rheumatoid arthritis. Indeed, this change formed the basis for the classification of the disease as atrophic arthritis by Goldthwait.⁹ Swain¹⁰ has noted the atrophy of the whole bony system in this type of arthritis. Howitt and Christie¹¹ emphasize the importance of the general progressive skeletal atrophy which they find demonstrable, before the onset of joint changes.

SUMMARY OF THE PATHOLOGICAL SIMILARITIES BETWEEN SCORBUTIC AND RHEUMATOID ARTHRITIS

It will be seen that there are many pathologic similarities between the experimental scorbutic and rheumatoid types of arthritis. Features in common include synovial proliferation and connective tissue pannus formation. In the capsular and periarticular tissues, connective tissue overgrowth is seen in both conditions. The hyaline streaks of fibrin usually found in association with the connective tissue hyperplasia of scorbutic arthritis, appear to correspond with the "fibrinoid" degeneration, which Klinge finds to be a basic lesion in the rheumatic diseases. Retrogressive changes in the articular cartilage are observed in both scorbutic and rheumatoid arthritis. In a few instances, fibrous tissue transformation of the subarticular marrow, noted by Nichols and Richardson in proliferative arthritis, has been seen in the scorbutic joints. General skeletal atrophy, most marked at bone ends, is seen in both the experimental and clinical arthritis. Muscle atrophy and degeneration occur in both conditions. Finally, fibrous nodules develop beneath the skin in experimental animals, that are remarkably like the early subcutaneous nodules of rheumatoid arthritis. One microscopic feature commonly but not constantly observed in rheumatoid arthritis is the presence of focal collections of lymphocytes in and about the synovial tissues. This change has been seen in only a few instances in the scorbutic joints and has never been a prominent feature. It is possible that if a more chronic process were produced experimentally, this lesion might be observed.

DISCUSSION

Scattered reports have directed attention to joint disabilities in the presence of vitamin C deficiency. Jackson and Moore¹² noted the prominence of joint manifestations in guinea pigs fed an exclusively milk diet. Smith¹³ observed that the first manifestations of scurvy in guinea pigs are swollen and tender joints. The diet employed by her consisted of a paste made of alfalfa meal and wheat flour with whole oats and water given *ad lib*. Howe¹⁴ fed guinea pigs rolled oats and fat free milk supplemented with small amounts of carrot and lettuce. By regulating the intake of carrots and lettuce he maintained the animals in a deficient state for periods of three months to a year. His interest was primarily in dental degenerative changes, but he states: "The usual joint affections occur to a marked degree, and when this condition has been maintained for a long time and the animals are restored to a normal diet, it is found that the legs have become fixed in an abnormal position. This seems to us to be more like rheumatism and arthritis deformans than many experimental conditions that have been called such." Stiner,¹⁵ in a paper entitled "Experiments on Rheumatic Diseases in Animals," observed that young guinea pigs fed sterilized food (e.g., hay, turnips, oats) and various kinds of prepared milk, developed joint swelling, disability and deformity. He recognized the vitamin C deficiency of the diet but was also inclined to ascribe a direct noxious effect to the pasteurized milk. He was impressed by the general similarity of the manifestations in the animals to the manifestations of rheumatism in man. It will be recognized that the experimental diets employed by the investigators cited are probably deficient in other food factors than vitamin C, including salts and other vitamins, although the outstanding deficiency was certainly of vitamin C.

GENERAL CONSIDERATIONS

Many of the epidemiological factors, previously considered,¹⁶ which apply to rheumatic fever, pertain also to rheumatoid arthritis. The evidence indicating the existence of latent scurvy and the factors relating to storage and utilization of vitamin C are equally pertinent. The observations suggesting that the vitamin C requirement may be enhanced by achlorhydria would appear significant in view of the relatively high incidence of this factor in rheumatoid arthritis. The data cited, indicating the depleting effects of fatigue and certain infections on the organic stores of vitamin C, suggest auxiliary mechanisms that might precipitate a significant deficiency state.

The impaired peripheral circulation, emphasized by Pemberton and Osgood¹⁷ in rheumatoid arthritis, would appear explainable on the basis of vitamin C deficiency. The pathology of chronic scurvy is dependent, to a considerable extent, upon the impairment of the capillary wall and attendant circulatory inadequacies.

The importance of acute infections and of focal infection, emphasized

particularly by Cecil¹⁸ and his school, is not denied. Indeed, the experimental data strongly suggest that certain infection may accelerate and aggravate the scorbutic arthritis, and in some instances, it would appear that the deficiency may, by lowering the resistance of the joint tissues to circulating bacteria, favor their lodgement and the development of a truly infectious (purulent) arthritis. Milder infections might occur with less virulent organisms.

Howitt and Christie¹¹ direct attention to the prodromal symptoms frequently preceding the onset of rheumatoid arthritis. These include loss of appetite, tachycardia, fall in blood pressure, a slightly raised temperature, sweating of the hands and feet, dermatographia, tremor, nervousness, loss of weight, an extreme degree of fatigue, disability, and vague muscular pains. It would seem significant that many of these symptoms are characteristic of latent scurvy.

There is a definite tendency among students of the subject, to consider rheumatoid arthritis a general constitutional disease with joint manifestations as its most serious feature. This is clearly evidenced by the reports of the American Committee for the Control of Rheumatism¹⁹ and of the Committee of the British Medical Association²⁰ as well as by numerous individual studies. The general atrophic changes often encountered in rheumatoid arthritis, involving skin, hair, fingernails, muscles and bony skeleton, have been particularly noted by Swain.²¹ Swollen, puffy, edematous gums are frequently seen in this disease. Swain²¹ observes: "The gums are spongy and teeth decay easily. The mouth resembles that of a scurvy patient."

Many writers have stressed the importance of nutrition, notably Goldthwait,²² Burnett and Ober,²³ Howitt and Christie,¹¹ Irons,²⁴ Fletcher,²⁵ Pemberton,²⁶ Rowlands²⁷ and Hall.²⁸ The latter notes: "We are constantly seeing patients with severe arthritis, who for months or years have been eating inadequate or deficient diets. In such cases, the diet has been the depleting factor." Rowlands,²⁷ and Fletcher and Graham²⁹ have presented indirect evidence that vitamin B deficiency may operate in the etiology of rheumatoid arthritis. The evidence is based essentially upon the frequent observation of atony of the musculature of the colon. Fletcher and Graham gave patients high vitamin diets with particularly generous amounts of vitamin B and observed improved tone in the bowel and frequently much clinical benefit. It is not improbable that vitamin B deficient states do indirectly contribute to development of arthritis. Nutritional inadequacies are likely to be multiple. Vitamin B deficiency appears to act largely through limitation of the voluntary food consumption by impairment of appetite. In this way, an inadequate vitamin C intake might follow in its wake, particularly if the food selection did not include the richer sources of this factor.

Although it is not the primary purpose of this paper to report clinical studies of rheumatoid arthritis which are in progress,³⁰ certain general facts

have emerged which appear worthy of comment. In the first place, careful inquiry into dietary habits of persons suffering from this disease has indicated that a very considerable number have been on faulty diets, and in many instances, surprisingly low in vitamin C containing foods. Further, capillary resistance tests (an index of latent scurvy) have shown, in general, low levels, and with the institution of high vitamin C containing diets, these levels have risen. Several cases reported here exemplify these findings.

CASE REPORTS

Case 1 S. T. B., white male, aged 42. On January 15, 1934, the patient thought that he had sprained his right ankle. The next morning, he found his knees, elbows, wrists and ankles were stiff. The left knee was considerably swollen and the other joints less so. He entered the San Francisco Hospital, Febr. 10, 1934, showing moderate swelling and pain in wrists, knees and the right ankle. Study of his dietary habits revealed striking inadequacies for several years due to unemployment. Cracked oats, bread, coffee, beans and stews formed the bulk of his foods. Just preceding the onset of arthritis, the diet had been somewhat more generous but still low in vitamin C. More than usual physical work and exposure immediately preceded the onset of arthritis. Capillary resistance tests (Dalldorf method) gave low readings. The dental condition was extremely bad with reddened, edematous gums. The patient was given the routine hospital diet with a daily supplement of one quart of orange juice. Improvement was rapid and recovery complete without further therapy. Four months later, the patient was found to have remained asymptomatic. The capillary resistance level had returned to normal.

The presence of vitamin C deficiency here can hardly be doubted. In fact, it appears that the patient probably suffered a scorbutic arthritis which, however, was clinically considered to be an early, relatively acute, rheumatoid type of arthritis.

Case 2 C. H., white female, aged 42, entered University of California Clinic, January 1, 1934, with a complaint of pain and swelling of right foot and ankle for past eight months. At the onset, she had an attack of pleurisy. Transient pains appeared in her elbows and ankles. A few days later, the pain in the left ankle became very severe. At about the fourth week, the ankle was said to be of a bluish-red color. At the clinic, the ankle showed a diffuse hard swelling with a yellowish area of discoloration at the medial aspect. Roentgen-ray examination revealed marked atrophy of the bone about the ankle joint. The roentgen-ray diagnosis was acute infectious arthritis. Diet analysis by an experienced nutritionist revealed a low intake of vitamin B and what was considered a very low intake of vitamin C. The capillary resistance test showed a surprisingly low strength. The ankle was placed in good position in a light ambulatory splint, and the patient returned to her home with diet instructions to supply a very generous amount of vitamin C. One month later, excellent improvement in the condition of the ankle was noted. The capillary resistance showed a moderate but definite elevation. A report of recent date indicates little or no residual disability.

Case 3 A. H., white male, sailor, aged 45, entered U. C. Hospital, March 1, 1935 with a typical erythema multiforme and a mild arthritis, dating back two weeks. On entry, examination showed swelling of knees with excess fluid, and some limitation of movement in shoulder. Dietary inquiry revealed generous and apparently adequate food intake including vitamin C up to five months ago, when the patient lost his job as

a merchant sailor Since that time, the patient had been on relief, receiving a small cash allowance He prepared his own food The caloric intake was relatively generous, but except for potato, practically no vitamin C-containing foods were consumed He ate little or no fresh fruit or vegetables in this period Capillary resistance tests were considered within normal limit Oral hygiene was poor, and the gums were puffy, red and edematous On March 3, 1935, the patient was started on daily doses of sodium ascorbate (250 mg) intravenously The following day, the left wrist was painful to movement, and there was thickening over the first metacarpal phalangeal articulation The erythema showed evidence of clearing March 7 Pain and swelling in knees were subsiding, and the wrist pain had gone Progressive clinical improvement ensued, which has persisted to date, in spite of the fact that a suppurative inguinal lymphadenitis has developed At the present, five weeks after entry, the skin is clear and patient is free of arthritis The general condition is improved and gums appear firmer The patient was given 7 daily doses of sodium ascorbate (250 mg each) intravenously, then doses three times a week for three weeks, following which he was advised to eat vitamin C-containing foods

Case 4 L H F, male, aged 34 This patient is one who had a chronic arthritis of the rheumatoid type with marked disability and deformity A more or less progressive development dated back to an onset 16 years previously Dietary habits indicated a moderately but not severely low intake of vitamins B and C-containing foods Capillary resistance tests gave strikingly low readings The gums were puffy, reddened and retracted The arthritic disability consisted in stiffness, deformity and pain in hands, wrists, elbows, feet and ankles The patient was instructed to take one pint of orange juice daily He has been on this regime for 15 months Gradually the capillary resistance has returned to a nearly normal level at present Although improved, it was distinctly low six months after onset of dietary regime Although he has had recurrent attacks of pain in one or more joints, the painful episodes are distinctly less frequent and less severe The patient considers his general sense of well being and arthritic condition distinctly improved

The writer does not wish to be guilty of the single-minded zeal warned against by Pemberton³¹ Indeed, he is in complete sympathy with a broad, unbiased approach to the problem, and realizes that many factors, some known, others not, lie in the background It is felt, however, that the evidence indicates that vitamin C deficiency may operate as an important factor in the etiology of some cases of rheumatoid arthritis, and that the concept is worthy of serious consideration

SUMMARY AND CONCLUSIONS

Subacute or chronic vitamin C deficiency in the guinea pig produces an arthropathy with manifold similarities to rheumatoid arthritis These include synovial proliferation, intra-articular pannus formation, periarticular fibrous tissue overgrowth, bone atrophy and subcutaneous nodules In certain instances, superimposed infection accelerates and accentuates the pathological process In this study, infection in the presence of adequate vitamin C nutrition failed to produce arthritis Brief evidence is presented that vitamin C deficiency may, by producing a locus of diminished resistance, also operate as a predisposing factor in the etiology of truly infectious (suppurative) types of arthritis The general atrophic changes found in rheumatoid arthritis involving bony skeleton, muscle and skin, are seen also in

chronic vitamin C deficiency Evidence indicating the probable clinical importance of latent scurvy, and the depleting effect of fatigue and certain infections on the organic stores of vitamin C, is noted Clinical data are cited that the nutritional habits are frequently imperfect preceding the onset and during the course of rheumatoid arthritis Experimental, epidemiological and clinical evidences afford the basis for the concept presented, that vitamin C deficiency may operate as a factor in the etiology of some cases classified as rheumatoid arthritis

REFERENCES

- 1 KLINGE, F, and GRIMM, N Das Gewebbild des fieberhaften Rheumatismus VI Mitteilung Der chronische Gelenkrheumatismus (Infektarthritis, Polyarthritis lenta) und uber "rheumatische Stigmata," *Virehow's Arch f path Anat*, 1932, ccxxviii, 646-712
- 2 DAWSON, M H A comparative study of subcutaneous nodules in rheumatic fever and rheumatoid arthritis, *Jr Exper Med*, 1933, lvi, 845-858
- 3 RINEHART, J F, CONNOR, C L, and METTIER, S R Further observations on pathologic similarities between experimental scurvy combined with infection and rheumatic fever, *Jr Exper Med*, li, 97-114
- 4 RINEHART, J F Does vitamin C deficiency play a role in rheumatoid arthritis? (Paper read before California Medical Association, May 1934)
- 5 KLINGE, F Das Gewebbild des fieberhaften Rheumatismus XII Mitteilung Zusammenfassende kritische Betrachtung zur Frage der geweblichen Sonderstellung des rheumatischen Gewebeschadens, *Virehow's Arch f path Anat*, 1932, ccxxviii, 344-388
- 6 NICHOLS, E H, and RICHARDSON, F L Arthritis deformans, *Jr Med Res*, 1909, vii, 149-221
- 7 FISHER, A G T Chronic (non-tuberculous) arthritis, 1929, Macmillan Co, New York
- 8 LIFWITMAN, L J, and JONIS, A B Fibrositis, 1915, William Heinemann, London
- 9 GOLDTHWAIT, J E Infectious arthritis, *Boston Med and Surg Jr*, 1904, cl, 363-371
- 10 SWAIM, L T Arthritis, *Pennsylvania Med Jr*, 1931, xxxiv, 535-537
- 11 HOWITT, F D, and CHRISTIE, W F The malnutrition factor in rheumatoid arthritis, *Lancet*, 1931, 1282-1287
- 12 JACKSON, L, and MOORE, J J Studies on experimental scurvy in guinea pigs, *Jr Infect Dis*, 1916, viii, 478-514
- 13 SMITH, E A A study of the alimentary tract in experimental scurvy (guinea pig), *Am Jr Physiol*, 1927, lxxx, 288-300
- 14 HOWE, P R Food in relation to teeth, *Jr Dental Res*, 1921, iii, 7-37
- 15 STINER, O Rheumatische Erkrankungen im Tierversuch, Mitteilungen aus dem Gebiete der Lebensmitteluntersuchung und Hygiene, 1929, vi, 1-8
- 16 RINEHART, J F Studies relating vitamin C deficiency to rheumatic fever and rheumatoid arthritis I Rheumatic fever, *ANN INT MED*, 1935, vi, 586-599
- 17 PEMBERTON, R, and OSGOOD, R B The medical and orthopedic management of chronic arthritis, 1934, Macmillan Co, New York
- 18 CECIL, R L Rheumatoid arthritis, *Jr Am Med Assoc*, 1933, c, 1220-1227
- 19 OSGOOD, R B Orthopedic aspects of chronic rheumatism or arthritis (including an outline of concept of the American Committee for the Control of Rheumatism concerning the disease commonly called chronic rheumatism or arthritis), *Jr Am Med Assoc*, 1930, xev, 992-995
- 20 Report of the British Medical Association Committee Causation and treatment of arthritis and allied conditions, *Brit Med Jr*, 1933, i, 1033-1052
- 21 SWAIM, L T Atrophic arthritis, *Rhode Island Med Jr*, 1923, vi, 51-55

- 22 GOLDTHWAIT, J E Arthritis—general considerations, *Am Med*, 1930, *xxxvi*, 589-592
- 23 BURNETT, F L, and OBER, F R Arthritis, anabolic nutrition and health, *Am Jr Med Sci*, 1934, *clxxxviii*, 93-109
- 24 IRONS, E E The treatment of chronic arthritis, *Jr Am Med Assoc*, 1934, *ciii*, 1579-1583
- 25 FLETCHER, A A The nutritional factor in chronic arthritis, *Jr Lab and Clin Med*, 1930, *vi*, 1140-1144
- 26 PEMBERTON, R Some metabolic and nutritional aspects of chronic arthritis, *Am Jr Digest Dis and Nutr*, 1934, *i*, 438-441
- 27 ROWLANDS, M J Rheumatoid arthritis is it a deficiency disease? *Proc Roy Soc Med*, 1927, *xx*, 41-68
- 28 HALL, F C Treatment of arthritis, *Am Med*, 1929, *xxxv*, 367-372
- 29 FLETCHER, A A, and GRAHAM, D The large bowel and chronic arthritis, *Am Jr Med Sci*, 1930, *clxxxix*, 91-93
- 30 Arthritis Committee, University of California Medical School (Unpublished observations)
- 31 PEMBERTON, R Work of American Committee for the Control of Rheumatism, present status of arthritis, *Med Jr and Rec*, 1933, *cxxxviii*, 359-363

THE EFFECTS OF CHRONIC DISEASE OF THE LIVER ON THE COMPOSITION AND PHYSICOCHEMICAL PROPERTIES OF BLOOD· CHANGES IN THE SERUM PROTEINS; REDUCTION IN THE OXYGEN SATURATION OF THE ARTERIAL BLOOD*

By ALBERT M SNELL,† M D , F A C P , *Rochester, Minnesota*

THERE are many problems in connection with chronic parenchymatous disease of the liver which have never been satisfactorily explained on an anatomic basis alone. For instance, it is difficult to understand why certain individuals with moderate or advanced degrees of nodular cirrhosis have minimal symptoms or none at all, cirrhosis is frequently discovered at operation or necropsy in cases in which there have not been any symptoms of it, and this has given rise to much discussion as to what compensatory processes are involved. While it is true that the liver possesses extraordinary powers of regeneration and a large functional reserve capacity, these facts do not fully explain the persistence of anatomic changes in the organ and the maintenance of normal or nearly normal health.

One also sees numerous examples of "toxic" or other types of cirrhosis, in which recovery takes place even after all of the signs and symptoms of late hepatic disease have developed¹³. In some of these individuals, as in the experimental animal, the liver apparently returns to a normal anatomic and physiologic state, in others, the liver retains the appearance of disease, but for all practical purposes it is functionally sound. The cirrhosis which is associated with splenic anemia is a case in point, it does not disappear after splenectomy, but the patient may be greatly improved in health by this procedure, and hepatic function may show only minor abnormalities when studied by means of appropriate tests.

These clinical observations, as well as numerous physiologic studies, lead one to believe that the liver is somehow concerned in the maintenance of the "internal environment" and that when under certain conditions it fails in this respect, a vicious circle is developed, leading to progressive disintegration of the hepatic parenchyma and further changes in the physiologic constants of the living organism. It is natural to search for such changes in the blood, since the liver is intimately connected with the production of certain of its constituents. The studies to be reported are concerned with the probable relation of the liver to the maintenance of the serum proteins and with the occurrence of changes in the oxygen content of arterial blood secondary to hepatic disease. It is apparent that changes in both of these physiologic constants have some bearing on the clinical

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935
From the Division of Medicine, The Mayo Clinic, Rochester, Minn

† With the technical assistance of Elizabeth Maclay, B A

manifestations of hepatic damage and that they may be in some manner related to the production of the "vicious circle" of progressive deterioration or destruction of the liver cells

SERUM PROTEINS IN HEPATIC DISEASE

The relation of the liver to the production of plasma proteins has been disputed, although it is generally agreed that fibrinogen is exclusively a hepatic product,¹⁷ it is not certain that serum albumin and serum globulin are manufactured in the liver alone. Direct proof is not available at present, but experimental data furnish some indirect evidence implicating the liver in formation of these substances.

Kerr, Hurwitz and Whipple^{27, 28, 29} in a series of papers (1918) reported that there was regeneration of the serum proteins following plasmapheresis and that the globulin was replaced more rapidly than the albumin. They noted that, after a 50 per cent depletion of serum proteins, regeneration took place in from five to seven days, which happened to be exactly the time required for regeneration of the liver cells after an episode of hepatic necrosis produced by carbon tetrachloride. It was also observed that phosphorus and carbon tetrachloride poisoning resulted in moderate decreases in the serum proteins, and that regeneration of the protein occurred slowly in the presence of hepatic injury or of an Eck fistula.

Sawada later observed a decrease in the albumin and an increase in the globulin content of the serum following experimental schistosomiasis, and in phosphorus, chloroform, and carbon tetrachloride poisoning, and Bollman has noted similar changes in experimental hepatic lesions produced by various substances. Fiessinger and Guthrie have shown a decrease in the total protein content of the serum after hepatectomy and a decrease in the total protein, with reversal of the albumin-globulin ratio after the production of an Eck fistula. Recent work (1934) from Whipple's^{25, 26} laboratory has given support to the theory that the liver is intimately concerned in the formation of serum proteins. These studies suggest that there is a reserve of protein-building material in the organism which is stored, at least in part, in the liver and which is probably at least 50 per cent albumin or albumin-producing material. Whipple and his coworkers also concluded that there is probably a dynamic equilibrium between tissue and plasma protein, in which equilibrium the stored material in the liver probably figures.

There is a long series of reports on the relation of hepatic disease to the level of serum protein, the first of which contained the observations of Gilbert and Chiray, and Grenet^{1, 2, 7, 8, 18, 20, 39, 40, 41, 42, 51, 57, 64} (1907). It has been observed repeatedly that in advanced chronic hepatic disease, there is frequently a moderate reduction in the total amount of serum protein, the diminution occurring chiefly in the albumin fraction, with reversal of the albumin-globulin ratio. In the less advanced cases, the albumin may be

only moderately reduced and the globulin actually increased, infection probably is responsible for the latter finding⁵² In any type of hepatic disease, however, the effects on the albumin-globulin ratio are much the same In advanced chronic hepatic disease, albumin-globulin ratios as low as 0.3 have been observed, in less serious types, the changes are not so marked or constant, and the ratio tends to return to normal as improvement takes place The data in a small series of selected cases observed during the last year are presented graphically in figure 1 These results are in accord with the

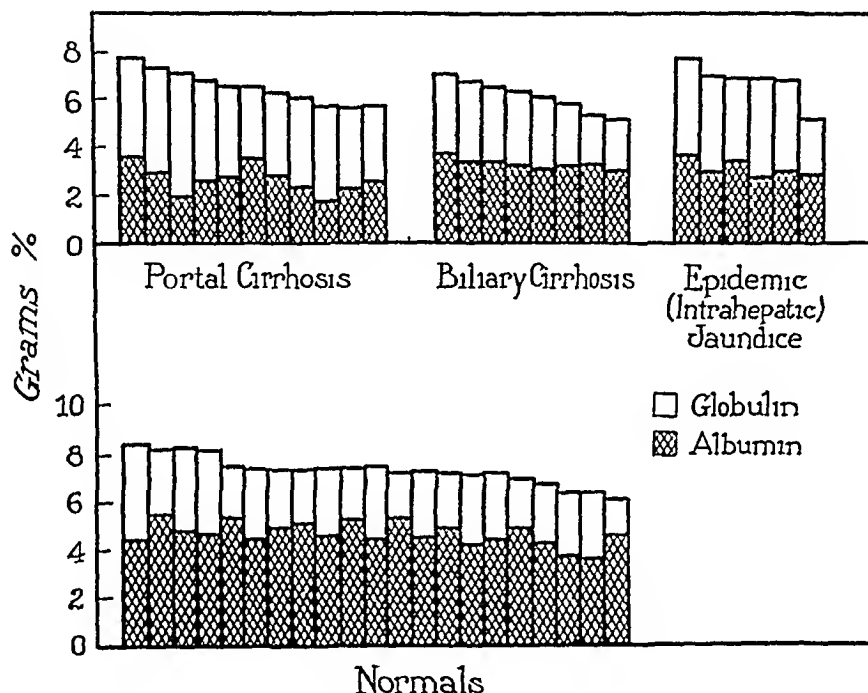


FIG 1 The serum proteins and albumin-globulin ratios in various types of hepatic disease

reports on clinical cases mentioned in the literature and also with those recently reported by Myers and Keefer³⁰ In a fairly large series of cases of all types of hepatic disease I have found only a few in which the normal albumin-globulin ratio was not disturbed, although the total proteins were not necessarily reduced The rapidity with which changes in the total protein and the albumin-globulin ratio may take place is rather striking, and repeated determinations on the same individual indicate that these changes may not be without some prognostic significance Peters and Eisenman have properly raised the objection that these variations in the serum proteins may be of nutritional origin, rather than being attributable to failure of production of protein in the liver However, the degree of malnutrition in many of the cases cited was not conspicuous, and the rapidity with which variations occur is not easily explained on a nutritional basis It has also been noted that in hepatic disease, feeding of protein has little effect on

either the total serum protein or on the albumin-globulin ratio. The amount of protein lost in ascitic or edema fluid does not seem to be a factor, Barnett and his collaborators noted one patient who lost an average of 10 gm of protein daily in the ascitic fluid over a long period of time and yet maintained the plasma proteins at a fairly constant although somewhat lowered level. In general, the clinical and experimental evidence related to lowered serum protein in cases of hepatic injury seems to indicate a failure of production of protein or protein-building substances on the part of the liver, with an altered equilibrium between circulating and stored protein. The fact that changes occur chiefly in the albumin fraction is in accord with the previously observed fact that it is formed less readily than globulin.^{6, 32}

The principal effects referable to the reduced albumin content of blood serum of patients with hepatic disease are obviously related to the production of ascites and edema. The "edema level" (4 to 5 gm per 100 cc) for the total serum proteins is not often reached, but the disproportionate reduction in serum albumin may reduce the osmotic pressure of blood serum sufficiently to produce transudation, especially in regions where venous stasis occurs. As Wells and his collaborators have shown by direct measurement, the specific osmotic pressure of serum is a linear function of its concentration of albumin, the globulin content is relatively unimportant. In malnutrition, edema may occur with values for serum albumin of less than 3 gm per 100 cc¹⁰, in the serum of nine of 11 patients with ascitic cirrhosis (figure 1), the value for albumin was 3 per cent or less. In the cases of obstructive biliary cirrhosis, and in those of intrahepatic jaundice, the albumin was at or near the 3 per cent "edema level," but not more than 4 per cent in any case. These patients had neither ascites nor appreciable edema. It should be noted that ascites in hepatic disease does not necessarily depend on the level of serum albumin alone, since one encounters readings of 3.5 to 4 gm per 100 cc in the presence of ascites, and lower figures in cases in which ascites is absent, such factors as portal venous stasis and chronic peritoneal irritation must also play an important part. The lowered serum albumin is a contributing factor only. Other effects of a lowered content of serum albumin on the organism are largely matters of conjecture, disturbances in general tissue nutrition may be produced by this means, but proof is lacking. One diagnostic procedure, the Takata-Ara reaction, may be dependent on variations in the content of serum protein, and especially on the relatively high values for globulin²³, a small experience with this test indicates that there is possibly some correlation between positive tests and reversed albumin-globulin ratios.

One may conclude that one of the fairly constant effects of parenchymatous hepatic disease is reduction in the serum albumin and reversal of the albumin-globulin ratio, that these changes are most probably related to deficient production of protein by the liver, and that for this reason they may have some diagnostic and prognostic significance, and finally, that the serum albumin is often at or near a level which makes the production of ascites and edema relatively easy.

REDUCTIONS IN THE OXYGEN SATURATION OF THE ARTERIAL BLOOD

My attention was first called to the possibility of anoxemia being a factor in hepatic disease by the work of Rich, who noted that in pernicious anemia there was atrophy of the cells around the central veins of the hepatic lobules, presumably the result of oxygen want. He showed subsequently that the same lesions were present after simple hemorrhage in experimental animals, and confirmed MacCallum's observations that this same type of atrophy was found in certain types of chronic passive congestion of the liver. Later Rich and Resnik showed that if animals were kept in an atmosphere low in oxygen, atrophy of the cells of the central portion of the lobule developed. Campbell and Rosin have made similar observations, and Loewy has noted certain physiologic and chemical changes in the liver under the same conditions. With these findings in mind, the possible relation of oxygen want to other chronic hepatic lesions was investigated.

Methods and Technical Considerations Arterial blood for analysis was obtained by arterial puncture from the brachial artery under local anesthesia with procaine. Venous blood was drawn, without stasis, from the median or the basilic vein. A sterile syringe containing 5 c c of sterile mineral oil, free of air bubbles but not previously evacuated, was used in collecting each specimen. Immediately after withdrawal, the blood was placed under mineral oil in a small beaker, and a few crystals of potassium oxalate in the beaker were mixed with the blood by gentle stirring with a small glass rod. Analysis of these samples was made for oxygen and carbon dioxide content, most of the analyses were completed within an hour, all were completed within three hours after the blood was drawn. In a few cases the determinations were repeated four to six hours later. This delay resulted, in each instance, in only slight increase (1 to 2 per cent) in the oxygen content of the oil-protected sample. Samples of blood used for determination of oxygen capacity were equilibrated with room air and at room temperature by rotating in a 150 c c separatory funnel for 15 minutes or longer, constant rotation of the funnel insured maximal exposure of the blood. The technic and apparatus used in determining oxygen and carbon dioxide in arterial and venous bloods were essentially those described by Van Slyke and Neill in 1924, using a modified oxygen absorption mixture as introduced by Van Slyke in 1927. Determinations were done in duplicate, simultaneously, on two machines of the closed manometer type. "Percentage saturation," more correctly stated as "percentage oxygenation," was calculated by dividing the oxygen content by the oxygen capacity, both content and capacity were expressed in volumes of oxygen in 100 c c of blood.

CASE REPORTS

Case 1 The first case studied was that of a man, aged 46 years, of pronounced alcoholic habits, who presented himself because of weakness, loss of weight, and jaundice of two months' duration. On examination the peculiar, dusky color of the

facies attracted attention, there seemed to be definite cyanosis in addition to visible jaundice. Examination of the lungs gave entirely negative results. The heart was slightly enlarged, the apex was felt just to the left of the nipple line. The pulse rate averaged about 100 beats per minute while the patient was at rest, and the patient was definitely dyspneic on slight exertion. The blood pressure, in millimeters of mercury, was 130 systolic and 90 diastolic. The liver was symmetrically enlarged and firm, the spleen could not be felt, and there was a small amount of free fluid in the abdomen. The urine was negative. There were 16 gm of hemoglobin per 100 c c of blood, as measured by spectrophotometric methods, corresponding to an oxygen capacity of 21.4 volumes per cent. The erythrocytes numbered 3,780,000, and the leukocytes 9,400 per cubic millimeter of blood, and the differential formula was normal. Examination of stained blood smears disclosed slight macrocytosis. A serologic test for syphilis was negative. Roentgenologic and fluoroscopic examinations of the chest revealed nothing of importance, except slight, diffuse widening of the aortic shadow. The urea, uric acid, and sugar content of the blood serum were normal. The bilirubin content of the blood serum was 4.4 mg per 100 c c. The fragility of the erythrocytes was normal. The liver functional test with bromsulphalein disclosed retention of dye, grade 4. A galactose tolerance test revealed excretion of 3.36 gm of reducing substance in five hours. There was definite oxygen unsaturation of the arterial blood, as is shown in table 1. Spectroscopic examination of the blood did not give evidence of methemoglobin or sulphemoglobin.

The patient was reexamined two months later. The slight cyanosis and jaundice were unchanged, and the liver was definitely smaller, but the anemia had increased somewhat, the concentration of hemoglobin was 11.1 gm per 100 c c of blood, corresponding to an oxygen capacity of 14.8 volumes per cent. The liver functional test with bromsulphalein gave evidence of retention of dye, grade 3. Careful reexamination of the lungs and heart by physical, roentgenologic, and fluoroscopic means did not give evidence of any definite pulmonary or cardiac lesion.

At the last examination, four months later, the patient was definitely dyspneic and orthopneic, and both the cyanosis and ascites apparently had increased somewhat. Again, no pulmonary or cardiac lesion could be demonstrated to account for the anoxemia. Saturation of the arterial blood with oxygen was even lower than before, and saturation of the venous blood, which previously had been within normal limits, was significantly reduced. Retention of bromsulphalein, grade 2, persisted. After inhalation of 50 per cent oxygen for 10 minutes, the arterial saturation of oxygen was only 88 per cent. It seemed possible that the cyanosis was connected in some way with the probable hepatic cirrhosis, since there were no cardiac lesions or lesions of the respiratory tract to explain the condition.

The patient died suddenly one month later, from a profuse gastrointestinal hemorrhage. Roentgenologic examination of the stomach previously had been negative, and it was assumed that the source of the hemorrhage was esophageal varices.

Case 2 The second patient, an obese man, aged 49 years, presented a typical clinical picture of portal cirrhosis, probably of alcoholic origin. An adenomatous goiter with mild hyperthyroidism, and a basal metabolic rate 25 per cent above normal also was present, but there was no demonstrable cardiac incompetence at any time. The oxygen content of the arterial and venous blood was determined before and after thyroidectomy, and again several months later, the results are noted in table 1. To conserve space, further details of the clinical course are omitted. Because of the complicating factor of the hyperthyroid state and the possible effect on the circulation, these data may not be admissible as evidence.

Case 3 This patient, a man, aged 58 years, presented a somewhat different situation, in which extraneous factors were fairly well eliminated. He also had a definite history of alcoholism. He presented himself at the clinic because of jaundice.

TABLE I
Repeated Determinations, with Particular Reference to the Administration of Oxygen, of Oxygen Content of the Blood
of Three Patients Who Had Portal Cirrhosis

Date	Ascites, grade	Serum bilirubin, mg per 100 c c	Bromsulphalein retention, grade	Oxygen, ca- pacity, volumes, per cent	Arterial oxygen		Venous oxygen		Remarks
					Content, volumes per cent	Saturation, per cent	Content, volumes per cent	Saturation, per cent	
<i>Case 1</i>									
3-28-33	1+	4.4	4	19.6	15.63	79.6	14.7	74.9	Portal cirrhosis, ascites, jaundice
5-21-33	1+	5.6	3	15.6	13.1	84.0	7.76	49.7	
9-12-33	2+	5.3	2	15.0	10.5	70.0	4.4	29.0	After 10 minutes in 50 per cent oxygen
<i>Case 2</i>									
2-6-34	1+	5.6	3	20.26	16.43	81.0	12.77	63.0	Portal cirrhosis, mild hypothyroidism
2-13-34		2.0	3	17.27	16.22	93.9	14.25	82.5	After 90 minutes in 60 per cent oxygen
2-28-34	0	3.6	3	14.9	13.6	91.2	11.4	76.5	After thyroidectomy
11-28-34	2+	3.4	3	19.3	17.0	88.0	8.9	46.0	Ascites and edema present
<i>Case 3</i>									
2-9-34	3	4.4	4	14.67	12.3	83.8	5.7	38.8	Portal cirrhosis, ascites, jaundice on admission
									Before paracentesis
2-14-34	1	4.7		13.95	11.97	85.8	6.2	44.4	After paracentesis
2-20-34*		3.9		13.86					
2-22-34	1+	3.8		13.3	12.44	92.9	9.0	67.8	Patient in 50 per cent oxygen

* Carbon monoxide capacity of blood 14.0 volumes per cent, iron content 29.4 mg per 100 c c

of five months' duration, and ascites and edema of two weeks' duration. Physical examination revealed a dropsical and jaundiced individual who was in poor general condition. The diaphragm was somewhat elevated, and a few inconstant, moist râles were heard at the bases of the lungs posteriorly. The abdomen was distended with fluid, and there was definite edema of the legs and genitalia. Examination of the heart revealed no objective findings of consequence. The systolic blood pressure, in millimeters of mercury, was 132, and the diastolic, 82. The pulse rate was 112 beats per minute. Visible collateral circulation was noted over the abdomen, and the liver was moderately enlarged. The patient was hospitalized immediately for further study.

Among the significant laboratory findings were definite macrocytic anemia, the value for hemoglobin was 10 gm per 100 c.c., corresponding to an oxygen capacity of 13.4 volumes per cent, and erythrocytes numbered 3,170,000 per cubic millimeter of blood. The urea content of the whole blood was 22 mg, and the bilirubin content, 4.4 mg per 100 c.c. Liver functional tests disclosed retention of bromsulphalein, grade 4. Electrocardiographic examination was negative. Roentgenologic examinations of the chest gave no evidence of appreciable increase in density at the bases of the lungs. The arterial oxygen saturation was reduced (table 1), and there was only slightly greater saturation after 4,000 c.c. of ascitic fluid had been withdrawn by paracentesis. There was, however, a slight rise in the oxygen saturation of the venous blood after this procedure. Following paracentesis, the cardiac output was 5.6 liters per minute (2.55 liters per minute per square meter of body surface). The blood was negative for methemoglobin and sulphemoglobin on spectroscopic examination. A few days after the second series of oxygen studies, a small area of congestion was made out in the base of the right lung, both by physical means and by roentgenologic examination. The patient was kept in an atmosphere containing 50 per cent oxygen for several days, in which time the chest cleared up entirely, and the arterial oxygen saturation rose to practically normal. Following a blood transfusion and another paracentesis, the patient was dismissed from the hospital considerably improved. He died, however, two months later in typical hepatic coma. Throughout his stay in the hospital the chest was examined daily for any lesion which might of itself tend to produce anoxemia, but with the exception of the small area of congestion previously referred to, there were never any findings of consequence. As has been noted, the original oxygen studies were made before and after paracentesis, while the chest was, for all practical clinical purposes, clear, although some edema of the alveolar walls could not, of course, be excluded.

COMMENT

With these three cases in mind, further study of the problem was begun, and determinations of oxygen were made on the arterial and venous blood of a series of patients who had portal cirrhosis, a group of controls was checked at the same time.

Of 20 persons studied, consisting of ambulant individuals of both sexes, chiefly healthy laboratory workers or patients who had peripheral vascular disease, the oxygen capacity of the blood ranged from 16.8 to 22.9 volumes per cent, with a mean of 19.6 volumes per cent. The arterial oxygen saturation varied from 90.8 to 98.4 per cent (average 94.7), the lowest reading was obtained on a patient who had thromboangitis obliterans and extensive phlebitis, moreover, some antecedent pulmonary infarction could not be absolutely excluded. Thirteen hospital patients, chiefly patients with complicated or recurrent peptic ulcers, cholecystic disease, or gastric carcinoma

without evident metastasis, were also examined. In this group, the oxygen capacity ranged from 16.0 to 23.2 volumes per cent, with a mean value of 18.4 volumes per cent, the average arterial oxygen ranged from 92 to 95 per cent, with a mean value of 93 per cent. As might be expected, the average venous saturation was slightly lower in the ambulant group (64.7 per cent) than in individuals who were at more or less complete rest in bed (67.6 per cent). The figures relative to the ambulant patients are similar to those given by Peters and Van Slyke, and by Harrop, for normal subjects, the results on patients who were confined to bed were slightly lower, a fact which may be explained by their inactivity, weakness, and possibly by a sluggish pulmonary circulation.

Data on the oxygen capacity, content and percentage saturation of arterial and venous blood in a group of 20 additional patients who had portal cirrhosis are given in table 2. It should be noted that five patients of the group (cases 14 to 18 inclusive) displayed only minor degrees of arterial oxygen unsaturation, that three of these had syphilitic cirrhosis, and that one of this group of three (case 11) was definitely anemic and had no ascites at the time of examination. In this case, however, there was definite oxygen unsaturation of the arterial blood (12.2 per cent) on light exercise. Another of this group of three (case 16) had had ascites intermittently for three years, but had remained in good general condition. The third (case 19) had had a recent profuse gastrointestinal hemorrhage and at the time of examination was very anemic. Of the remaining 15 patients, two (cases 4 and 5) demonstrated arterial oxygen unsaturation of more than 15 per cent, and both were in very poor condition, death occurring within a few weeks after the examination in question. Somewhat more than half of the whole group had a percentage oxygenation (85 to 90 per cent) of arterial blood, corresponding to that which is found in normal persons living at high altitudes. Jaundice apparently was not essential for the presence of anoxemia, the amount of ascitic fluid and the degree of abdominal distention in the group also varied considerably, without apparent effect on the degree of oxygen unsaturation of arterial blood. The actual percentage of hemoglobin present, and consequently the oxygen capacity, did not appear to be a factor, although the arterial blood of the most anemic patient in the group was of approximately normal oxygen saturation. With improvement in the patient's condition (two cases), normal values for oxygen saturation were obtained. The acuteness of the hepatotoxic process, its severity, and the general condition of the patient seemed to be paralleled roughly by the percentage oxygen saturation of the blood in any given case.

In portal cirrhosis, there remains some probability that in certain cases the anoxemia is related to the ascites, to the subsequent elevation of the diaphragm and atelectasis of the lungs, and also, possibly, to clinically unrecognizable edema of the alveolar walls. However, certain patients represented in table 1 had definite ascites, and yet the arterial oxygen unsaturation in these cases fell within the range of the ambulatory control group, the

TABLE II
Blood Oxygen Content of Patients Who Had Portal Cirrhosis

Case	Oxygen capacity, volumes per cent	Arterial oxygen		Venous oxygen		Serum bilirubin, mg per 100 c c	Bromsulphalein retention	Remarks
		Content, volumes per cent	Satura- tion, per cent	Content, volumes per cent	Satura- tion, per cent			
4	28.2	21.2	77.4	20.8	13.7	4.0	2	Polycythemia vera, hepatitis with portal thrombosis, hepatic and renal insufficiency (verified at necropsy)
5	13.1	10.74	82.6	9.35	71.9	12.5		Alcoholic cirrhosis, ascites, jaundice, poor condition
6	11.4	9.92	87.0	5.84	51.2	1.0	2	Cirrhosis, ascites (surgically verified)
7	15.0	13.1	87.3	11.1	74.0	3.8	3	Alcoholic cirrhosis, ascites, jaundice
8	15.3	13.7	87.3	10.3	67.3	1.4	3	Alcoholic cirrhosis, ascites
9	16.4	14.5	88.1	13.85	84.4	9.4	3	Alcoholic cirrhosis, ascites, grade 1, slight jaundice
10	18.3	16.15	88.4	12.45	68.1	1.3	2	Alcoholic cirrhosis with ascites (surgically verified), figures verified on two subsequent days
11	18.6	16.6	89.2	10.8	58.0	5.8	4	Alcoholic cirrhosis, ascites
12	20.5	18.27	89.2	8.13	39.6	8.0		Alcoholic cirrhosis, ascites, jaundice
13	17.7	16.0	90.3	12.2	68.9	4.4	4	"Compensated" cirrhosis (alcoholic)
14	11.8	10.9	92.3	3.3	28.0	1.0	2	"Compensated" cirrhosis (syphilitic), arterial saturation 87.8 per cent after light exercise
15	13.2	12.2	92.4	8.7	63.9	11.0		Portal cirrhosis (verified at necropsy, after death from mesenteric thrombosis)
16	16.5	15.6	92.7	14.5	87.8	2.0	2	Syphilitic hepatitis, ascites of three years' duration
17	21.9	20.4	93.1			1.5	2	Portal cirrhosis, etiology unknown
18	4.23	3.97	93.8	0.9	21.0	1.0	4	Syphilitic cirrhosis, recent hemorrhage
19	11.4	9.4	82.4	7.2	65.9	9.1	4	Toxic cirrhosis with ascites, jaundice, hepatic insufficiency
20	14.8	13.3	89.8	12.4	63.1	10.0		After paracentesis and transfusion
	14.15	12.3	86.9	5.88	41.9	1.0	3	Banti's disease (surgically verified), portal cirrhosis
	12.15	11.96	96.0					One year later, much improved, toxic cirrhosis
21	19.6	17.3	88.3	11.8	60.2	15.0		Ascites, jaundice, small pleural effusion
22	19.3	16.7	86.5			1.5	2	Ascites, portal cirrhosis, surgically verified. In O ₂ arterial oxygenation 96 per cent
23	24.68	21.75	88.1	17.07	69.5	1.0	4	Polycythemia vera, portal cirrhosis
	23.7	22.0	92.8	20.0	84.3	1.0	3	One year later, marked symptomatic improvement

principal factor which these patients had in common was that the condition was chronic, and the general condition of all these individuals was reasonably good. The sudden death of one patient in the group, from mesenteric thrombosis, allowed for verification of the hepatic lesion at necropsy, a definite nodular type of cirrhosis was found. An opportunity also presented itself, at this time, to study the purely mechanical effect of ascites on two other patients, one a man, aged 50 years, who had active tuberculous peri-

tonitis and a normal liver, verified both by appropriate functional tests, and at operation, and the other was a woman, aged 40 years, who had chronic glomerulonephritis, ascites, and edema, in both cases, the arterial oxygen unsaturation was not appreciably greater than that noted in other cases in which patients were bedfast, the percentage saturation of the arterial blood in the first case was 91.3 per cent, and in the second, 93.2 per cent.

In order to distinguish further between the possible mechanical factors involved and the effect of the hepatic disease per se, a second and third group of cases were studied, including patients who had various types of acute parenchymatous hepatic damage and also patients who had prolonged obstructive jaundice, attributable to stricture of the common duct, neoplasm, and stone. In only one case of this group was ascites present. The results are given in tables 3 and 4. It will be noted that in three of the six cases in which jaundice of the "intrahepatic" type was present (table 3), mod-

TABLE III
Blood Oxygen Content of Patients Who Had Intrahepatic Jaundice

Case	Serum bilirubin, mg per 100 c c *	Oxygen capacity, volumes per cent	Arterial oxygen		Venous oxygen		Remarks
			Content, volumes per cent	Satura- tion, per cent	Content, volumes per cent	Satura- tion, per cent	
24	12	15.8	14.6	92.4	Not obtained		"Toxic" jaundice of unknown origin
25	30	16.5	15.2	92.1	11.3	68.4	Infectious (epidemic) jaundice
26	20	18.0	16.4	91.0	8.0	44.4	Epidemic jaundice
27	15	18.3	16.3	89.0	9.7	53.0	"Toxic" jaundice of unknown origin
28	7	18.0	16.5	87.3	8.4	44.4	"Toxic" jaundice of unknown origin
29	15	19.3	16.8	86.0	9.0	46.6	Chronic hepatitis (cinchophen)

* Highest recorded level in each instance

erate degrees of unsaturation of the arterial hemoglobin were observed, the most marked change was noted in a case of severe hepatitis attributable to cinchophen.

In the nine cases of obstructive jaundice and various degrees of hepatitis, cholangitis, and biliary cirrhosis (table 4), the blood of only one patient was of normal oxygen saturation, the blood of five other patients gave values which averaged about 5 per cent below normal, and in the remaining three, strikingly low values were obtained. Two of these patients had stricture of the common duct of long duration, with extreme degrees of obstructive biliary cirrhosis, a third patient (case 37) had very marked cholecystitis, hepatitis, and cholangitis, and was deeply jaundiced at the time of examination, in this case, the normal figures obtained one month

TABLE IV

Blood Oxygen Content of Patients Who Had Obstructive Jaundice

Case	Serum bilirubin, mg per 100 c c *	Oxygen capacity, volumes per cent	Arterial oxygen		Venous oxygen		Remarks
			Content, volumes per cent	Satura- tion, per cent	Content, volumes per cent	Satura- tion, per cent	
30	18	12 17	11 57	95 0	9 2	75 5	Stricture of common duct, good general condition
31	4	17 2	15 8	91 8	11 5	66 8	Stone in common duct, biliary cirrhosis, jaundice, slight ascites
32	15	16 7	15 2	90 8	12 1	72 4	Carcinoma of pancreas with obstructive jaundice
33	11	19 6	17 5	89 5	8 3	42 3	Stone in common duct, biliary cirrhosis
34	9	9 67	8 6	88 9	3 07	31 7	Stricture of common duct of long duration, marked biliary cirrhosis with hemorrhagic tendency
35	32	9 2	7 6	82 6	6 1	31 7	Stricture of common duct and hepatic insufficiency, extremely ill
36	22	16 5	13 18	79 8	12 5	75 7	Marked biliary cirrhosis, carcinoma of gall-bladder with metastasis, portal thrombosis
37	34	2/6 18 5 3/12	15 3	82 7	5 8	31 4	Severe cholangitis and hepatitis before operation
38	14	17 95 17 2 20 7	17 5 15 5 17 5	95 2 90 1 80 4	8 5	49 5	After operation, much improved Carcinoma of pancreas and cirrhosis, grade 3 Coma hepaticum (two weeks later)

* Highest recorded level in each instance

after operation coincided with the striking clinical improvement which had occurred in the interval. In one other case (case 33), a postoperative determination of the arterial and venous oxygen content was made, but little change was noted from the earlier figure, this was to be expected in view of the advanced hepatic fibrosis and biliary cirrhosis, which followed six months of obstructive jaundice caused by stone in the common duct. Case 38 was of special interest because of the low percentage oxygenation of the arterial blood noted while the patient was in hepatic coma, a point which will be mentioned later.

In the whole group of patients who had hepatic disease, the degree of oxygen unsaturation of the arterial blood seemed to reflect the general condition of the patient, numerous exceptions were noted, but in general a normal or slightly reduced oxygen saturation of the arterial blood was found only when the patient's general condition was better than the average, a very low figure for oxygen saturation usually indicated a condition bordering on hepatic insufficiency. These observations on clinical subjects are supported to a very considerable extent by studies on experimental animals, the details of which will be reported subsequently by Bollman and me.

The possible causes of anoxemia in these cases require some discussion. There are, according to Peters and Van Slyke, four types of anoxia (anoxemia) (1) anoxic anoxia, a condition produced by high altitudes, chronic pulmonary or bronchial lesions, and congenital cardiac anomalies which allow for admixture of arterial and venous blood, (2) anemic anoxia, attributable to a decrease in the concentration of hemoglobin in the circulating blood, this may be attributable to anemia from various causes, or to the presence of inactive compounds of hemoglobin, (3) stagnant anoxia, attributable to failing circulation, this may be present in such conditions as cardiac failure and venous obstruction, (4) histotoxic anoxia, attributable to conditions in which the tissue cells are unable to take up oxygen from the circulating blood, as in poisoning with cyanides and alcohol. In the first type, anoxic anoxemia, there is a reduced percentage oxygenation of arterial blood, in the second, anemic anoxia, the percentage saturation of hemoglobin in arterial blood is normal, but the low content of functioning hemoglobin produces a low arterial and venous oxygen tension. In stagnant anoxia, the hemoglobin is normal in amount and the percentage oxygen saturation of the arterial blood is within normal limits, but the oxygen tension of the venous blood is low, in histotoxic anoxia, the arterial and venous hemoglobin are normally saturated with oxygen.

The results of the studies reported above, on oxygen content of the blood of patients with hepatic disease, indicate that the anoxemia is of the anoxic variety and that the cause may be tentatively assigned to some change in the lung or to a failing circulation. However, the latter could hardly be an important factor, especially if patients do not have ascites and edema. In dropsical patients it is not so easily excluded, however, in three such cases the cardiac output was normal or elevated, and in none of our cases was there any evidence of preexisting cardiac disease. The arterial blood pressures in the whole group of cases studied were within the limits of normal. Attention is drawn to the lungs chiefly because of the observed increases in the oxygen saturation of arterial blood after inhalation of oxygen. As Lundsgaard and Van Slyke have noted, the fact that one can relieve visible cyanosis and increase the percentage saturation of arterial blood to normal levels by this means is fairly good evidence that the seat of the anoxemia lies in deficient absorption of oxygen from the alveoli. There were no constant or characteristic pulmonary findings in these cases, even on repeated physical and roentgenologic examination nothing of consequence could be made out in the chest except in the occasional case. The factor of shallow respiration, suggested by Meakins, may play a part, but it hardly seems sufficient to explain the whole picture. Vital capacity was somewhat reduced in certain of our cases, but this might be expected in any disease process of equal severity. Data obtained at necropsy, as one might expect, show some evidence of pulmonary lesions, in a series of 40 consecutive fatal cases of chronic parenchymatous hepatic disease, which Foley has reviewed, in about 80 per cent there was edema of the pulmonary bases, grade 1 or 2,

and terminal bronchopneumonia or hydrothorax, singly or in combination. On the basis of pathologic evidence, the pulmonary lesions were considered to be essentially terminal phenomena, and there was little to indicate that they played a part in the production of anoxic anoxemia during life. Edema of the alveolar walls, of minor degree, may cause reduction in arterial oxygen saturation, as Ruhl has shown by the production of histamine shock in experimental animals, similar changes cannot be absolutely excluded in hepatic disease, and may constitute a major factor in the production of anoxemia.

Is it possible that changes in the hemoglobin itself could produce anoxemia of this type? There are adequate reasons to assume that the liver is concerned with formation of hemoglobin. The work of Whipple⁶³ and his collaborators indicates that "the liver participates in active fashion in the preparation of parent substances for hemoglobin production" and that in severe hepatic injury, with anemia, these hemoglobin-production factors can be shown by biologic assay to be greatly reduced. Similar low hemoglobin-production values have been demonstrated in cirrhosis by this same means,⁵⁰ especially if hepatic insufficiency had been present before death. This is in accord with the observed macrocytic anemia of chronic hepatic disease, the presence of which has been repeatedly noted and recently reviewed by Fellingner and Klima. Although the failure of hemoglobin-production under these conditions is evident, it is pure hypothesis to assume that the hemoglobin may be altered in a qualitative fashion, since it is generally supposed that hemoglobin of man is a substance of constant composition,^{5, 11} and that its structure is not altered in disease. Such well known forms of inert hemoglobin as methemoglobin, sulphhemoglobin, or carbon monoxide hemoglobin do not enter into consideration, since they can be demonstrated by spectroscopic examination, and in the cases studied the spectroscopic appearance of the blood was normal. The close correspondence between the values for hemoglobin and the figures for oxygen capacity of the blood in these cases eliminates, for practical purposes, the possibility of the formation of nitrobenzol hemoglobin or related compounds.³³ Other forms of inactive hemoglobin are largely hypothetical and can be excluded from consideration by the same means. However, Ray, Ray and Stimson, Stimson, and Stimson and Hrubetz in a series of papers, have discussed the question of a non-oxygen carrying hemoglobin which appears in the blood of rabbits after splenectomy. They also noted that after partial hepatectomy of rabbits, there was a discrepancy between the total pigment of blood and its ability to transport oxygen, and they called attention to a change in the spectroscopic appearance of blood under these conditions.

There remains, finally, the possibility that in hepatic disease the hemoglobin does not function normally as a respiratory pigment. For practical purposes, only two methods of study of the nature of hemoglobin are available, spectroscopic examination and examination of the dissociation curve of oxyhemoglobin in the specimen of blood in question. The former

method having failed to identify any known abnormal forms, Adams and I have attempted to utilize the latter method in the hope of identifying some variation in the type of hemoglobin produced by the diseased liver. It is known that the dissociation curves of hemoglobin are different in different species, and that there are also different temperature coefficients for oxygen exchange in different species.¹⁶ Species variations in the specific ability of a particular hemoglobin to combine with various mixtures of carbon monoxide and oxygen are also recognized.¹⁵ These variations are thought to be attributable to alterations in the globin fraction, this component of the molecule probably is specific for any given species.

The form of the dissociation curve of normal oxyhemoglobin, under standard conditions, has been established by Barcroft, the blood of normal individuals which have been studied, using methods of double equilibration

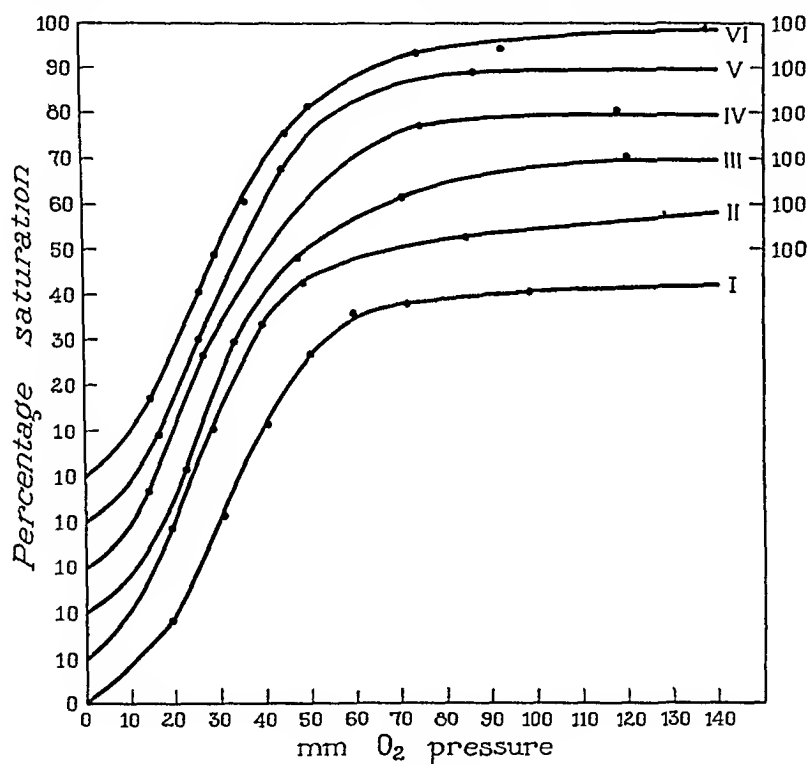


FIG 2 The dissociation curve of oxyhemoglobin in various types of hepatic disease (I) syphilitic cirrhosis, anemia, (II) portal cirrhosis, (III) portal cirrhosis, polycythemia, (IV) cholangitis, hepatitis, (V) splenic anemia, portal cirrhosis, (VI) normal

similar to those described by Austin and his collaborators, shows a dissociation curve which falls along that drawn by him. The dissociation curves of blood taken from patients who have advanced hepatic disease will be described in more detail in a subsequent report, it suffices to say that the curves which have been obtained on specimens examined to date show little change from Barcroft's normal (figure 2). This is almost certainly true for bloods which contain little or no excess of bilirubin, in the blood of

jaundiced individuals and experimental animals some minor changes are noted. In blood from both jaundiced and non-jaundiced patients and animals, however, no changes have been so far observed in the dissociation curve of oxyhemoglobin which have a direct bearing on the degree and type of anoxemia under discussion. Whether the blood of a patient who has hepatic disease is definitely polycythemic, or very anemic and diluted, as it may be after hemorrhage, the dissociation curve is the same, although the amount of oxygen which is given off at any given oxygen tension may vary greatly because of the great discrepancy in the total content of hemoglobin (figure 3). Richards and Strauss have previously noted that the dissociation curves of anemic and polycythemic blood are similar. Under standard conditions in the very anemic patient, however, the element of anemic anoxia is important, as figure 3 shows. The behavior of the dissociation curve of oxyhemoglobin of patients who have hepatic disease must, of course, be studied at different carbon dioxide tensions before the strict normality of the hemoglobin in these cases can be established. Such studies are in progress at present. It should be noted, parenthetically, that the carbon dioxide content of both arterial and venous blood was determined in a number of cases in this series, and reductions which were in general agreement with the degree of anoxemia were obtained.

There are other possible alterations in the physical character of the blood in hepatic disease which may have a bearing on the rate of oxygenation in the lung. Alterations in concentration of the blood and in surface tension, such as are known to occur in jaundiced blood, blood concentration,⁴⁶ and variations in the permeability of erythrocytes to oxygen may be important in affecting the rate of passage of oxygen from the alveoli of the lung to the hemoglobin within the erythrocytes. All laboratory workers are familiar with the altered physical character of blood in hepatic disease, particularly if jaundice is present, and these changes, although neither measurable nor understood, may be important in the solution of the problem.

The following possible explanations for the anoxemia noted in hepatic disease are still under investigation: (1) that there are changes in the physical character of the blood which retard the rate of its oxygenation in the lung, (2) that there are hypothetical changes in the physiologic behavior of hemoglobin which can be shown only by a consideration of the time required for its complete oxygenation, (3) that the behavior of the pulmonary alveoli as a site for oxygenation is altered in some manner, possibly by changes in the alveolar wall, with resultant difficulty in diffusion of oxygen (Brauer's pneumoniosis)³⁵, and finally, (4) that the engorged or contracted liver, with its mechanically altered blood flow, may decrease the rate of filling of the right auricle and indirectly reduce the rate of blood flow through the pulmonary capillaries, thus reducing the speed at which blood can be oxygenated. As Marie Krogh has noted, a reduced pulmonary blood flow results in a slow moving layer of blood along the capillary wall, with a more rapidly moving

axial stream, under such circumstances, it is not difficult to see how the rate of diffusion of oxygen into blood might be reduced

Whatever the explanation of this anoxemia may be, it seems likely that it may have some definite effect on the observed symptomatology of hepatic disease and on the progress of the hepatic lesion itself The hepatic facies, with its characteristic muddy, subicteric hue, may owe at least a part of its

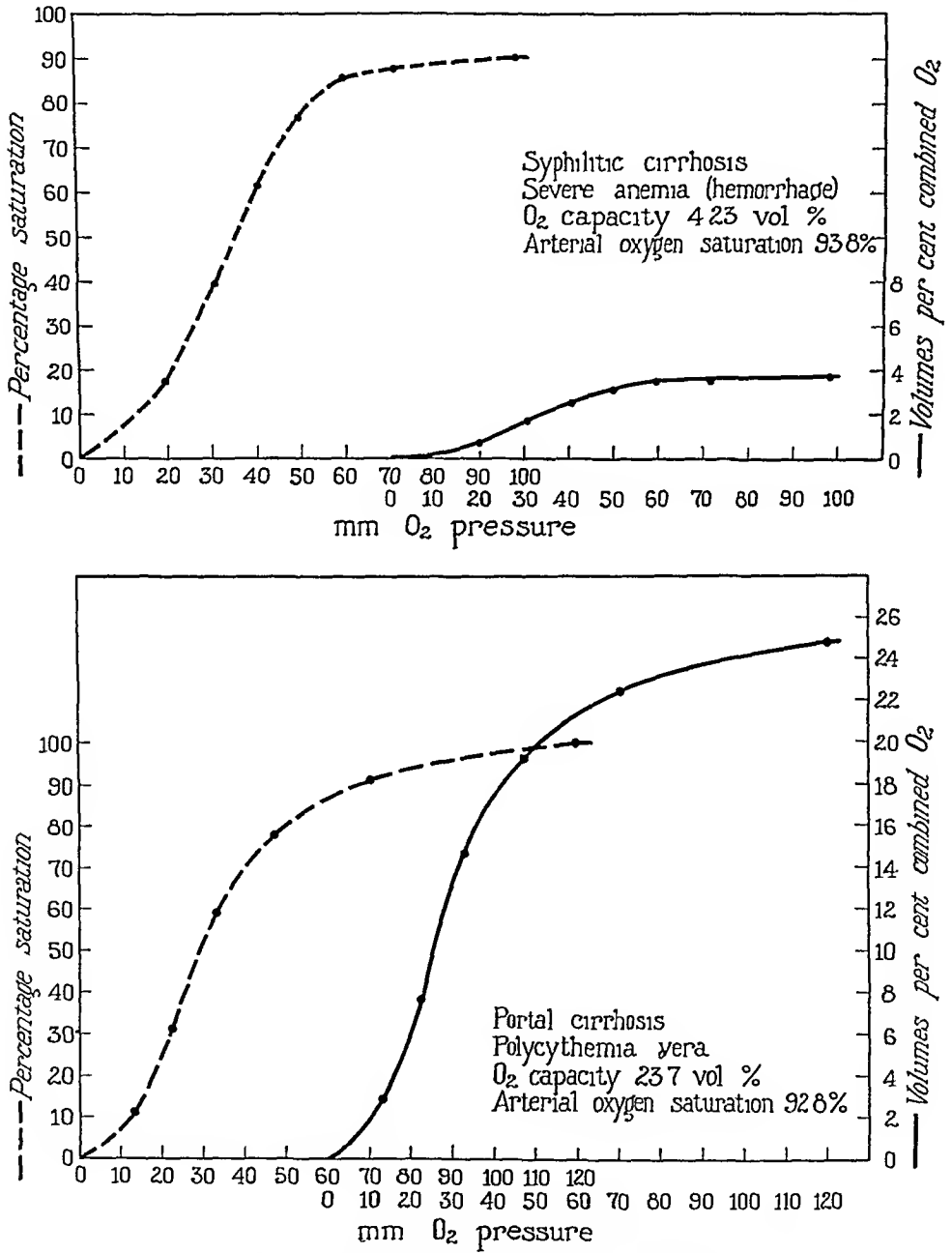


FIG 3 The dissociation curve of oxyhemoglobin and the relative amounts of oxygen in combination at various oxygen tensions, two patients are represented Above, anemia was present, below, polycythemia

familiar color to the presence of considerable quantities of reduced hemoglobin in the capillary blood. Baicroft's description of the Cholos on Cerro de Pasco could be used almost verbatim in describing the appearance of a patient with chronic hepatic disease. The clubbed fingers, which are a feature of juvenile cirrhosis, and which may occasionally be observed in adults who have cirrhosis, are probably attributable to a decreased supply of oxygen to peripheral tissues. Lassitude, fatigue, and insomnia, similar to that seen in mountain sickness, are common in hepatic disease, and it is possible that in both conditions the basis for these symptoms may be the same. The respiratory and cardiac symptoms noted at high altitudes (palpitation, dyspnea, periodic breathing), as well as the gastrointestinal symptoms (nausea, vomiting, anorexia), also have been observed in association with cirrhosis. The accumulation of lactic acid in the blood, which was recently commented on by Roth and me, may well be a sequel of deficient tissue oxygenation, and the lactic acidemia of hepatic disease may be quite comparable to that observed at high altitudes. Finally, the symptoms of hepatic coma which are referable to the central nervous system may be caused in part, or at least aggravated, by the anoxemia²⁴. Hitzenger has made a similar suggestion in regard to the psychic changes of congestive heart failure. Stupor or coma, convulsions, the so-called pyramidal tract syndromes and the host of neurologic signs which may be encountered in hepatic insufficiency are not greatly different from those which have been observed with unmixed anoxic states. In one case, in which the patient was in profound hepatic coma, a 20 per cent oxygen unsaturation was noted in the arterial blood, although a previous examination of this same individual had shown a figure not greatly reduced from the normal.

The probable effect of the reduced arterial oxygen saturation on the liver itself is obviously of considerable importance, since under conditions of anoxemia, either anoxic or anemic, definite atrophy of the central portion of the hepatic lobule takes place. The protective effect of oxygen against hepatotoxic substance, as shown by Goldschmidt, Ravdin, and Lucke, and the low tolerance of the experimental animal to carbon tetrachloride in the presence of low oxygen tensions⁹ are more pertinent observations, so far as the clinical subject is concerned. It seems likely that the factor of anoxemia may hasten the deterioration of the hepatic parenchyma in some cases, the low oxygen tension of the hepatic arterial blood producing further atrophy of hepatic cells, and also rendering the parenchyma subject to toxic influences which ordinarily could be withstood without difficulty.

The anoxemia may also contribute its share to the production of ascites and edema, as Landis showed by direct observations on the mesentery of the frog, lack of oxygen increased the rate of filtration fourfold, and allowed the passage of proteins through the capillary wall. The anoxemia may also add to the difficulty of maintaining a normal circulation, hearts dilate at high altitudes, and artificial cardiac dilatation may be induced in experimental animals by lack of oxygen. Possibly the phenomenon of "decompensa-

tion" in hepatic disease may be related to circulatory weakness, together with an increased rate of filtration of fluid through capillary walls

Finally, the question of compensatory mechanisms for this anoxemia must be considered. In certain of these cases, as in normal persons at high altitudes, there is a fall in the bicarbonate content of blood, an increase in cardiac output, and an accelerated respiration, the erythrocytosis which is so important a part of acclimatization to high altitudes does not appear, in spite of the stimulus of anoxemia, probably because of the failure of production of hemoglobin-building factors, except in the rather rare instances in which polycythemia and cirrhosis²² occur jointly in the same individual

SUMMARY

It may be said that there are no constant demonstrable changes in the lung or circulation which explain the anoxemia observed in cases of advanced hepatic disease, although minor degrees of edema of the alveolar walls cannot be excluded, that such mechanical factors as ascites and abdominal distention are not necessary for its production, and that to date it has been impossible to demonstrate any variations in the physiologic behavior of hemoglobin sufficient to explain the difficulty with which the blood of these patients takes up oxygen. So far as the effect of anoxemia on the symptoms and course of the disease is concerned, it suffices to say that anoxemia, if of considerable degree and duration, can have only one effect and that this would be an unfavorable one. It would also appear that the patient who has a chronic hepatic lesion is poorly equipped to adjust himself to even the less severe degrees of anoxemia because of the limitation in production of hemoglobin. Although the evidence is admittedly incomplete, there is much to suggest that anoxemia is at least one of the factors on which a vicious circle of progressive disintegration of the hepatic parenchyma is established.

BIBLIOGRAPHY

- 1 ABRAMI, P, and ROBERT-WALLICH. Modifications du serum sanguin au cours des cirrhoses du foie avec ascite. Inversion du rapport sernes-globulines, *Compt-rend Soc de biol*, 1929, ci, 291-293
- 2 ATCHILFY, D W, LOEB, R F, BENEDICT, E M, and PALMER, W W. Physical and chemical studies of human blood serum. III. A study of miscellaneous disease conditions, *Arch Int Med*, 1923, xxi, 616-621
- 3 AUSTIN, J H, CULLEN, G E, HASTINGS, A B, MCLEAN, F C, PETERS, J P, and VAN SLYKE, D D. Studies of gas and electrolyte equilibria in blood. I. Technique for collection and analysis of blood, and for its saturation with gas mixtures of known composition, *Jr Biol Chem*, 1922, liv, 121-147
- 4 BARCROFT, J. The respiratory function of the blood. Part I. Lessons from high altitudes, 1925, Cambridge University Press, 200 pp
- 5 BARCROFT, J. The respiratory function of the blood. Part II. Hemoglobin, 1928, Cambridge University Press, 200 pp
- 6 BARKER, M H, and KIRK, E J. Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, *Arch Int Med*, 1930, lv, 319-346

- 7 BARNETT, C W, JONES, R B, and COHN, R B The maintenance of a normal plasma protein concentration in spite of repeated protein loss by bleeding, *Jr Exper Med*, 1932, *lv*, 683-693
- 8 BARNETT, T I, DONDS, E C, and ROBERTSON, J D A study of plasma-protein loss with edema but without proteinuria and its bearing on the concept of nephrosis, *Lancet*, 1930, *ii*, 1006-1008
- 9 BOLLMAN, J L Studies on the experimental production of ascites (Unpublished data)
- 10 BRUCKMAN, F S, and PRITTS, J P The plasma proteins in relation to blood hydration V Serum proteins and malnutritional or cachectic edema, *Jr Clin Invest*, 1930, *viii*, 591-595
- 11 BUTTERFIELD, E E Über die Lichtextinktion, das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und Krankhaften Zuständen, *Ztschr f phys Chem*, 1909, *lxii*, 173-225
- 12 CAMPBELL, J A Concerning the problem of Mount Everest, *Lancet*, 1928, *ii*, 84-86
- 13 CHABROL, E, and COLLET, J La curabilité de l'ascite dans les cirrhoses atrophiques du foie, *Bull et mem Soc med d hop de Par*, 1934, *iii*, 700-701
- 14 FELLINGER, K, and KLIMA, R Lebereirrhose und Anamen, *Ztschr f klin Med*, 1934, *cxlvi*, 547-567
- 15 FIESSINGER, N, and GOTHIE, S L'évolution de l'équilibre albumine-globuline du serum apres l'hépatectomie totale et le fistula d'Eck chez le chien, *Compt-rend Soc de biol*, 1933, *cxii*, 1053-1055
- 16 FOLEY, M P Unpublished data
- 17 FOSTER, D P, and WHIPPLE, G H Blood fibrin studies IV Fibrin values influenced by cell injury, inflammation, intoxication, liver injury, and the Eck fistula Notes concerning the origin of fibrinogen in the body, *Am Jr Physiol*, 1922, *lxviii*, 407-431
- 18 GILBERT, A, and CHIRAY, M Diminution des substances albumineuses du serum sanguin chez les cirrhotiques aseitiques, *Compt-rend Soc de biol*, 1907, *lxiii*, 487-488
- 19 GOLDSCHMIDT, S, RAVDIN, I S, and LUCKE, B The effect of oxygen in prevention of hepatic necrosis produced by volatile anesthetics, *Arch Pathol*, 1934, *xlvi*, 593-594
- 20 GRFNET, H Diminution des albumines du serum sanguin chez les hepatiques, *Compt-rend Soc de biol*, 1907, *lxiii*, 552-553
- 21 HARROP, G A, JR The oxygen and carbon dioxide content of arterial and of venous blood in normal individuals and in patients with anemia and heart disease, *Jr Exper Med*, 1919, *xxx*, 241-257
- 22 HARROP, G A, JR Polycythemia, *Medicine*, 1928, *vii*, 291-344
- 23 HEATH, C W, and KING, E F The Takata-Ara test in the diagnosis of liver disease, *New Eng Jr Med*, 1934, *ccxi*, 1077-1081
- 24 HITZENBERGER, K Über Störungen des Bewusstseins bei Kreislaufkranken infolge Sauerstoffmangels, *Wien klin Wchnschr*, 1933, *xlvi*, 865-869
- 25 HOLMAN, R L, MAHONEY, E B, and WHIPPLE, G H Blood plasma protein regeneration controlled by diet I Liver and casein as potent diet factors, *Jr Exper Med*, 1934, *lix*, 251-267
- 26 HOLMAN, R L, MAHONEY, E B, and WHIPPLE, G H Blood plasma protein given by vein utilized in body metabolism II A dynamic equilibrium between plasma and tissue proteins, *Jr Exper Med* 1934, *lix*, 269-282
- 27 KERR, W J, HURWITZ, S H, and WHIPPLE, G H Regeneration of blood serum proteins I Influence of fasting upon curve of protein regeneration following plasma depletion, *Am Jr Physiol*, 1918, *xlvi*, 356-369
- 28 KERR, W J, HURWITZ, S H, and WHIPPLE, G H Regeneration of blood serum proteins II Influence of diet upon curve of protein regeneration following plasma depletion, *Am Jr Physiol*, 1918, *xlvi*, 370-378
- 29 KERR, W J, HURWITZ, S H, and WHIPPLE, G H Regeneration of blood serum proteins III Liver injury alone liver injury and plasma depletion the Eck fistula combined with plasma depletion, *Am Jr Physiol*, 1918, *xlvi*, 379-392

- 30 KROGH, M The diffusion of gases through the lungs of man, *Jr Physiol*, 1915, xlii, 271-300
- 31 LANDIS, E M Micro-injection studies of capillary permeability III The effect of lack of oxygen on the permeability of the capillary wall to fluid and to the plasma proteins, *Am Jr Physiol*, 1928, lxxviii, 528-542
- 32 LINDER, G C, LUNDGAARD, C, and VAN SLIKE, D D The concentration of the plasma proteins in nephritis, *Jr Exper Med*, 1924, xxxix, 887-920
- 33 LOEB, R F, BOCK, A V, and FITZ, R Acute nitrobenzol poisoning with studies on the blood in two cases, *Am Jr Med Sci*, 1921, cli, 539-546
- 34 LOEWY, A Über das Verhalten der Leber unter Luftverdunnung, *Biochem Ztschr*, 1927, cxlxxv, 287-319
- 35 LUNDGAARD, C, and VAN SLIKE, D D Cyanosis, *Medicine*, 1923, ii, 1-76
- 36 MACĚLA, I, and SLIŠKAR, A The influence of temperature on the equilibrium between oxygen and haemoglobin of various forms of life, *Jr Physiol*, 1925, lv, 428-442
- 37 MACCALLUM, A B Quoted by Rich
- 38 MEAKINS, J C Observations on the gases in human arterial blood in certain pathological pulmonary conditions, and their treatment with oxygen, *Jr Path and Bacteriol*, 1921, xxiv, 79-90
- 39 MYERS, W K, and KEELER, C S Relation of plasma proteins to ascites and edema in cirrhosis of the liver, *Arch Int Med*, 1935, lv, 349-359
- 40 MYERS, W K, and TAYLOR, F H L Hypoproteinemia probably due to deficient formation of plasma proteins a study of one case, *Jr Am Med Assoc*, 1933, ci, 198-200
- 41 PELLEGRINI, G L'azione della sostanza tiroidea sulle proteine e sulla pressione colloid-osmotica del sangue e sulla diuresi nella cirrosi epatica con ascite, *Arch di Patolog e Clin Medica*, 1934, xiii, 413-438
- 42 PETERS, J P, and EISENMAN, A J The serum proteins in diseases not primarily affecting the cardiovascular system or kidneys, *Am Jr Med Sci*, 1933, cxlxxvi, 808-833
- 43 PETERS, J P, and VAN SLIKE, D D Quantitative clinical chemistry Volume I Interpretations, 1931, Williams and Wilkins, Baltimore, 1264 pp
- 44 RAY, G B Chemical studies on the spleen II Changes in hemoglobin following removal of the spleen, *Am Jr Physiol*, 1928, lxxvi, 138-144
- 45 RAY, G B, and STIMSON, B B Observations on the chemical activity of the spleen I The relation of the spleen to methemoglobin in the blood, *Am Jr Physiol*, 1927, lxxvi, 62-73
- 46 RAY, G B, THOMAS, C I, and STRONG, J E The oxygenation of concentrated versus normal bloods, *Jr Clin Invest*, 1933, xii, 1051-1062
- 47 RICH, A R The pathogenesis of the forms of jaundice, *Bull Johns Hopkins Hosp*, 1930, xlvii, 338-377
- 48 RICH, A R, and RESNIK, W H On the mechanism of jaundice following pulmonary infarction in patients with heart failure, *Bull Johns Hopkins Hosp*, 1926, xxxviii, 75-76
- 49 RICHARDS, D W, JR, and STRAUSS, M L Oxy-hemoglobin dissociation curves of whole blood in anemia, *Jr Clin Invest*, 1927, iv, 105-126
- 50 ROBSCHKEIT-ROBBINS, F S, and WHIPPLE, G H Hemoglobin production factors in the human liver II Liver degeneration, cancer, cirrhosis, and hepatic insufficiency, *Jr Exper Med*, 1933, lvi, 653-670
- 51 ROSIN, A Morphologische Organveränderungen beim Leben unter Luftverdunnung, *Beitr z path Anat u z allg Path*, 1928, lxxx, 622-639
- 52 ROWE, A H The albumin and globulin content of human blood serum in health, syphilis, pneumonia, and certain other infections, with the bearing of globulin on the Wassermann reaction, *Arch Int Med*, 1916, xviii, 455-473
- 53 RUHL, A Über Störungen des Sauerstoffdurchtritts in der Lunge, *Arch f exper Path u Pharmakol*, 1930, cxviii, 282-303

- 54 SALAFSFN, H A Variations in the plasma protein in non-renal conditions, *Acta med Scandm*, 1929, lxxii, 113-123
- 55 SAWADA, T Biochemical investigation of the blood in cases of experimental disturbance of liver function Report II Liver function and protein metabolism, *Japan Jr Gastro-Enterol*, 1931, iii, 38-45
- 56 SNELL, A M, and ROTH, G M The lactic acid of the blood in hepatic disease, *Jr Clin Invest*, 1932, vi, 957-971
- 57 STARLINGER, W, and WINANDS, E Über das Verteilungsverhältnis der zirkulierenden Eiweißkörper im Verlaufe krankhafter Zustände III (Erkrankungen der Blut bildenden und zerstörenden Organe und der Leber, bosartige Geschwulste, Leukämie, Granulom, Magendarmgeschwür, Gastro-enteritis, Diabetes, und andere Erkrankungen der innersekretorischen Organe), *Ztschr f d ges exper Med*, 1928, lx, 185-238
- 58 STIMSON, B B Changes in the oxygen capacity of the blood pigment of rabbits following splenectomy, *Jr Biol Chem*, 1927, lxxv, 95-99
- 59 STIMSON, B B, and HRUBETZ, M C Changes in the oxygen capacity of the blood pigment of rabbits following partial hepatectomy, *Jr Biol Chem*, 1928, lxxviii, 413-415
- 60 VAN SLYKE, D D Note on a portable form of the manometric gas apparatus and on certain points in the technique of its use, *Jr Biol Chem*, 1927, lxxiii, 121-126
- 61 VAN SLYKE, D D, and NEILL, J M The determination of gases in blood and other solutions by vacuum extraction and manometric measurement, *Jr Biol Chem*, 1924, lxi, 523-573
- 62 WELLS, H S, YOUMANS, J B, and MILLER, D G, JR A formula and nomogram for the estimation of the osmotic pressure of colloids from the albumin and total protein concentrations of human blood sera, *Jr Clin Invest*, 1933, vii, 1103-1117
- 63 WHIPPLE, G H Anemia, liver function, and hemoglobin production, *Proc Calif Acad of Med*, 1932-1933, 81-102
- 64 WIENER, J H, and WIENFR, R E Plasma proteins, *Arch Int Med*, 1930, xli, 236-265

HYPOTHYROIDISM A COMMON SYMPTOM

By ROGER I. LEE, M.D., F.A.C.P., *Boston, Massachusetts*

THE task to which I have set myself may be stated as follows: concentrating on a very small part of the endocrine system, I have tried with the aid of clinical tests and clinical experience to formulate some conclusions which are not at variance, I hope, with the best and soundest of theory and experimental data, and which have the virtue, I trust, of a firm basis on clinical facts. If anyone finds in this paper something exciting, fantastic or in the slightest degree revolutionary, I have signally failed in my purpose.

Some of us can remember the eager search for the cases of cretinism and of myxedema. It was the period when the findings at the postmortem table dominated medical thought almost without challenge. Generally speaking, all distributed function, physiological or chemical, was related as a matter of course to gross or microscopic anatomical changes. If actual changes were not demonstrable, it was a defect in technique, not in the theory. The prevailing thought of the times was entirely out of sympathy with any notion of transitory functional changes without evident organic change, or with the notion of mild persistent disturbances of any sort which could not finally be solved post mortem. In fact, our ideas of clinical medicine were largely the reconstructed pictures from the autopsy table.

To be sure, there were imaginative individuals who rebelled at this tyranny of morbid anatomy. One of the unfortunate effects of the early stages of emancipation from the rule of pathology was found in the fantastic and uncontrolled utterances of some of these in the field of endocrinology, which made this field a kind of plague spot in clinical medicine. However, the increasing influence of physiology, chemistry and also of bacteriology has had the effect of changing markedly the attitude of the best current clinical thought. Attention has shifted from the end stage of disease (and indeed of life) towards the early phases of disease. Functional disturbances were studied with newly developed methods and techniques. Now we find a situation in which functional studies are sometimes carried on with (unfortunately) total disregard of morbid structural changes.

These functional studies have now reached a point at which intelligent attention can be directed towards thyroid dysfunction of a degree far less than those clinical states known as cretinism, exophthalmic goiter, and myxedema. In the laboratory new types of scientists have appeared, working with new methods, new materials, and all kinds of animals.

Clinical data were rapidly collected. The simple formula that a high basal metabolic rate equalled an operation, and that a low basal metabolic rate equalled thyroid administration, and that the results of both of these

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

equations meant cure, was early discarded. Gradually we have begun to organize, digest and classify our data and experiences. Here I shall omit all reference to the over-active function of the thyroid gland and shall confine my attention exclusively to the dysfunction which represents the apparent under-activity of the thyroid gland. Furthermore, in this discussion we shall eliminate all cases of organic disease of the endocrine system and also such cases of frank clinical disorders of the thyroid as myxedema and corresponding disorders of the other members of the endocrine system. It is perhaps open to argument whether a more exact and more suitable title might not be "Low Metabolic Rate, a Common Symptom." In truth the low metabolic rate is usually the determining factor in the discussion. However thyroid therapy has had an important rôle in these observations. In some instances basal metabolic rates have been ignored and thyroid administration employed. Again, the basal metabolic rate has frequently seemed to serve rather as a first approximation and not as an exact test. Consequently the old term, hypothyroidism, has been retained.

Certainly some families have many instances of dysfunction of the thyroid gland. These can often be related to general glandular unbalance. In addition to this, we sometimes find a persistently low metabolic rate, which may be taken roughly as evidence of hypothyroidism, in a substantial proportion of the members of a family. Many of these people seem entirely well. Such individuals do not conform to any particular type. They do not correspond to any notion of early or latent myxedema. They are as often thin as stout. The skin may be moist, the hair fine and glossy, and the pulse may be rapid. In others, there seems to be no connection between their particular ailments and the low thyroid activity, and furthermore, the administration of thyroid extract in various ways does not help the symptoms. In a small group thyroid therapy with the elevation of the basal metabolic rate to normal or a low normal figure seems to be associated with an improvement in general well-being.

By far the commonest association with a low metabolic rate (and by that I mean less than minus 15 per cent) is the condition perhaps most clearly designated as debility, when, of course, not associated with fever or growing neoplasm. The thought at once suggests itself that the thyroid gland shares in the general dysfunction of all the organs in the body, and that perhaps the lowered thyroid function is a general indicator of the total bodily function. However, there seems to be no precise parallelism between hypothyroidism and debility. Furthermore, the administration of thyroid and the apparent correction of the hypothyroidism may vary in the subjective effect on the patient from no result to a result indicating an apparent cure. Curiously enough the patient sometimes behaves differently under apparently similar conditions. One patient had a history of recurrent episodes of nervous fatigue or perhaps nervous exhaustion. In one of these episodes, the basal metabolic rate was as low as minus 40 per cent. Previous determinations had given low figures but near the line of normal. When

her rate was minus 40 per cent, energetic thyroid therapy was accompanied by a rapid restoration to satisfactory well-being. In subsequent episodes of similar symptoms, the basal metabolic rate was never again markedly low, and experimental thyroid therapy was never accompanied by any substantial improvement. In the various debilitated states due to many causes, some known and some unknown and often mixed, we have had similar experiences. As in many of the cases of familial hypothyroidism, these examples of hypothyroidism associated with debility present as a group none of the stigmata of myxedema. Actually most of the patients have been thin, and tachycardia of a mild degree has been common. Perhaps a substantial gain in weight has been the outstanding objective result of thyroid therapy in the successful cases. Subjectively the outstanding beneficial result has been improvement in general well-being. It should be emphasized again that apparently similar cases yield both successes and failures.

At one time thyroid therapy gained considerable favor in the treatment of chronic arthritis. Certainly, hypothyroidism is a frequent symptom of the associated debility of chronic arthritis, but presumably it is an associated symptom of the debility and not a causative factor. Of course, the correction of any symptom is indicated, and the subjective improvement thereby resulting, while varied, may be eminently satisfactory.

Our ideas are as yet far from clear as to the relation of the symptom of hypothyroidism to mental states. Doubtless, in many mental states there is an associated debility which in turn may be associated with the hypothyroidism of debility. On the other hand, it is becoming more evident that the individuality of a man with his physical, mental, nervous and behavior patterns, which all combine to make up his individual self and personality, is somehow closely linked with the structure and function of the endocrine glands, which of course represent the influence of heredity, environment, training and disease. Of course the thyroid gland is only one of the links of the chain of endocrine glands. Moreover, the relation of the thyroid and indeed of the whole endocrine system to various normal and abnormal mental states is not at this time clearly and definitely evident.

The interrelationship of the thyroid and some of the other endocrine glands is often demonstrable. Hypothyroidism is associated at times with female sterility, and thyroid therapy may be followed by pregnancy. Likewise, hypothyroidism may be seen in adolescence and in the menopause, and thyroid therapy may be distinctly beneficial. Its action is presumably indirect. The present advances in our knowledge of the various hormones may be fairly designated as exciting. In the experimental field the ability to achieve extraordinary results is literally breath-taking. It may well be that the near future has in store for us the solution of the complicated interrelationship of the endocrine glands. At this moment it seems that the rôle of the thyroid, so easily even if roughly tested, and when insufficient so easily restored by a simple therapeutic agent, may become perhaps relatively

insignificant Just now, all endocrine roads lead to the pituitary, but for how long!

Probably attributable to some defect in these general glandular inter-relationships, with perhaps debility as a further factor of possible importance, are a number of conditions which often but not always present evidence of hypothyroidism Among these are amenorrhea or disturbed menstrual function, the various vasomotor disturbances, perhaps notably vasomotor rhinitis, some of the odd irregular slight fevers, some of the allergic states, some of the dermatoses, etc In some of these, there is a definite hypothyroidism Even when this exists, thyroid therapy is often not beneficial It is undoubtedly inept to consider the hypothyroidism as the direct causative agent The hypothyroidism may better be regarded as a symptom Time does not permit of any elaboration of this variegated and miscellaneous group It is only mildly helpful to our understanding of the situation to bring out that there is a family factor in some of these cases, a possible endocrine relationship in others, a presumable association with a debilitated state in another group and that some may be early or atypical manifestations of that clinical entity, which, when fully developed, we call myxedema There are deep pitfalls for idle speculation and loose logic It may even be too rash to claim that the dry skin on which a dermatologic lesion develops is a possible manifestation of early or latent myxedema Certainly the intricate mysteries of vasomotor rhinitis are baffling Here too we find in apparently similar cases the same discrepancies, namely those with and those without hypothyroidism and furthermore those which yield to treatment and those which do not Again it is to be repeated that there is no precise parallelism between the level of the low basal metabolic rate and the success of thyroid therapy As might be expected the lowest rates, in general, are often associated with the best therapeutic results, but excellent therapeutic results are sometimes obtained by the administration of thyroid to patients with essentially normal basal metabolic rates

In further substantiation of these general views, the fact must be noted that thyroid therapy at times cannot be tolerated by these patients Experience shows there are cases in which the administration of all the usual preparations of thyroid gland either (1) does not restore the basal metabolic rate to normal, (2) does not benefit the patient or (3) cannot be tolerated on account of such untoward symptoms as headache, palpitation, nervousness, etc

Theoretically and experimentally the therapeutic administration of other glandular therapy has much to commend it in many of these groups of cases under discussion Certainly a case of frank hypothyroidism, which is resistant to usual thyroid therapy, may well serve for clinical experimentation in glandular therapy At present adequate clinical data are lacking for even tentative generalizations However, there is a promise of other potent glandular therapeutic agents which time may show may supplement or even supplant thyroid therapy

Hypothyroidism seems rarely to be a disease entity, but certainly, a common symptom. It is rather one of the fragments that make up the temporary or permanent pattern of the functional entity of the individual. As a fragment in a pattern it may have important relationships, most notably with the other endocrine glands. Presumably variations from the usual standard of the individual are more significant than variations from an arbitrary standard. In this respect there is some similarity to variations in blood pressure and especially to our interpretation of hypotension. All the theoretical, experimental and clinical data indicate that while hypothyroidism is only a symptom it is, nevertheless, a symptom which should be and can be frequently satisfactorily treated.

CLINICAL RELATIONSHIPS OF BLOOD CHOLESTEROL WITH A SUMMARY OF OUR PRESENT KNOWLEDGE OF CHOLESTEROL METABOLISM¹

By LEWIS M HURVATHAL, M D , F A C P , and HAZEL M HUNT, A B ,
Boston, Massachusetts

ALTHOUGH much has been written about cholesterol, little is actually known of its metabolism. The amount in the blood and various organs is known, points of secretion and excretion have been located, and its various forms have been identified, yet its true function in the body is pretty much a mystery. While the determination of blood cholesterol has clinical value, there is still much to be learned regarding the behavior of cholesterol in the body under normal and pathological conditions.

Cholesterol itself is an unsaturated secondary alcohol, water insoluble, and although associated intimately with fat metabolism it is not a true lipid. The cholesterol present in the body is in part derived from that contained in ingested animal food, but the greater part is formed by synthesis within the organism. It is not derived from vegetable foods as plants are incapable of cholesterol synthesis.¹

The following chart indicates the paths of cholesterol in the body as known at the present time.

The functions which have been ascribed to cholesterol are as follows:²⁻⁴

- 1 A constituent of the framework of cell because of its stability to ordinary chemical change
- 2 A protective substance in cells, exerting its effect as
 - An anti-toxic, anti-hemolytic and anti-infectious agent
 - An insulator of the central nervous system
 - A conditioning constituent of the skin
- 3 A conveyor of fatty acids to and from fat deposits
- 4 A facilitator of fat absorption

From the clinical point of view we are interested chiefly in the causes of variations in blood cholesterol, in the reasons for abnormal cholesterol deposits, especially in atherosclerosis, and in the mechanism of formation of cholesterol gall stones.

Even though we know comparatively little concerning the metabolism of cholesterol in the body, it is, nevertheless, possible to suggest how abnormal variations might arise. The following possibilities are suggested:

- 1 Abnormal synthesis beyond normal tolerance or destruction,

* Read at the Philadelphia meeting of the American College of Physicians, May 3, 1935
From the Medical Department of the Lahey Clinic and Chemical Laboratories of the New England Deaconess Hospital, Boston, Massachusetts

- 2 Abnormal affinity of tissues for cholesterol, causing retention, including phagocytosis ³,
- 3 Abnormal precipitation or liberation,
- 4 Hemoconcentration or dilution ³⁵,
- 5 Failure of destruction,
- 6 Failure of elimination ³

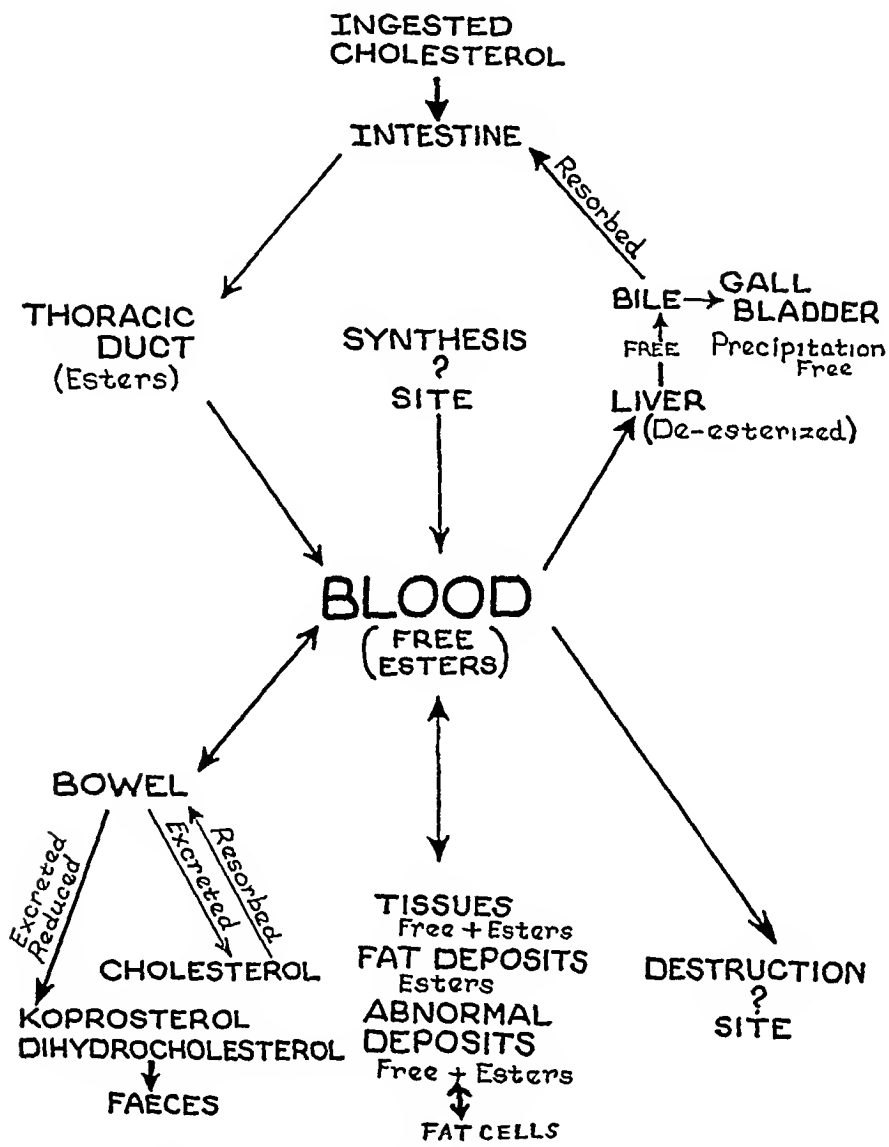


CHART 1 Cholesterol paths in the body (This chart is derived from the work of Windaus, Thannhauser, and Schonheimer abroad and Bloor, Speery and others in this country)

An attempt will be made here to correlate these possible abnormalities in the cholesterol mechanism with clinical states wherein cholesterol metabolism appears to be disturbed

MECHANISM OF CHOLESTEROL DEPOSITS

Cholesterol exists in the blood as such and also as cholesterol esters. The ester fraction of the total cholesterol under normal conditions varies from 40 to 60 per cent of the total. Likewise in the tissues, the cholesterol-ester ratio is of about the same proportion. In the blood cholesterol is thought to be present in colloidal suspension or linked with blood proteins. Almost all abnormal cholesterol deposits are associated with groups of fat or foam cells which are supposedly of reticulo-endothelial origin. There are two theories regarding the mechanism of abnormal cholesterol deposits.

- 1 Precipitation of cholesterol in the blood, phagocytosis there by the reticulo-endothelial cells, which thus become fat cells, and migration of these cells into the tissues, where they may degenerate, thus liberating cholesterol¹⁵

- 2 Infiltration of tissues by cholesterol because of their altered permeability due to disease, and ingestion in the tissues by reticulo-endothelial cells of the deposited cholesterol, the fat cells thus forming at the site where they are found⁴

ATHEROSCLEROSIS

Atherosclerosis is not necessarily a senile disturbance⁴. While we cannot expect to overcome senility, there should be hope of preventing premature arteriosclerosis^{5, 19}. Aside from hereditary, infectious and pressure phenomena, the evidence for a causal relation of cholesterol to atherosclerosis may be summarized as follows:

- 1 Atherosclerotic plaques contain cholesterol, the amount of which increases with the extent of atherosclerosis⁶

- 2 The cholesterol content of the blood increases with age and with the extent of atherosclerosis^{7, 8, 9, 10, 13}

- 3, Atherosclerosis analogous to human atherosclerosis may be produced in rabbits by feeding cholesterol in large or small amounts^{11, 14, 15, 16, 9, 21}

- 4 Atherosclerosis is more frequent in conditions such as diabetes mellitus and myxedema in which there is an abnormally¹⁴ high cholesterol content in the blood^{5, 17, 19}

No definite conclusion may be drawn in regard to dietary differences of races on the present data^{6, 18}. Individual differences of diet within the race must be considered along with other predisposing or restraining causes.

It is of interest that it has been noted in the experimental production of cholesterol atherosclerosis that the simultaneous administration of dried thyroid or potassium iodide with cholesterol will prevent the occurrence of atherosclerosis^{20, 21}. European investigators^{9, 22, 23} see in this the rationale for the time honored use of potassium iodide and more recently of thyroid extract in the treatment of clinical arteriosclerosis. Rosenthal⁶ has warned against the use of iodine, but its widespread use over many years would suggest that its dangers are insignificant.

Diets made up exclusively of animal foodstuffs with high fat content will

increase the cholesterol of the blood,²⁵ and a vegetable diet has been found to decrease the blood cholesterol in xanthomatosis.³ The ability to tolerate cholesterol must vary in different individuals. It is conceivable therefore that in the presence of an inadequate cholesterol tolerance of whatever cause, a diet high in cholesterol may hasten the development of human atherosclerosis, particularly if such predisposing causes as diabetes, hypertension or toxic or nervous influences are present. In other words, predisposing causes pave the way for cholesterol deposits, and one might assume that the less cholesterol available, the less the atherosclerotic change.

The part cholesterol plays in atherosclerosis may be belittled, but much remains to be learned by clinical observation and experimentation, both of which have not kept pace with experimental work on animals.

XANTHOMA AND XANTHOMATOSIS

Skin xanthoma and xanthelasma contain cholesterol and fatty deposits. Fat or foam cells are conspicuous in these lesions.²⁷ Hypercholesterolemia is a frequent finding in xanthomatosis with or without the presence of diabetes with which it is so commonly associated. Adequate treatment of an associated diabetes may cause absorption of the xanthomatous lesions.^{17, 26, 33} Schonheimer³ has shown in one carefully studied case of hypercholesterolemia and xanthomatosis that the retention of cholesterol was due to a defect in excretion. The high total cholesterol value was due to the ester fraction. On a strictly plant diet the total cholesterol content of the blood was markedly lowered, the change occurring entirely in the ester content. Wile, Eckstein and Curtis⁶² believe that cholesterol is only a secondary factor in xanthoma formation. Several cases reported by them had normal blood cholesterol values. Low caloric diets were most successful in reducing xanthomatous deposits in their cases.

Xanthomatosis may occur in the bones and other tissues as well as in the skin.⁵⁸ Such conditions too are known to be associated with extensive accumulation of fat cells. In these diseases, too, the blood cholesterol may be elevated.^{58, 63} Desiccated thyroid may have a favorable influence upon the absorption of these lesions, and should be more often given a trial.

With the disappearance of some xanthomata following treatment and the reversion of atheromatous changes in animals,²⁸ and possibly in humans,⁴ the possibilities of low or cholesterol-free diets should be further investigated. In the authors' experience a diet free from animal-derived foods is not disagreeable and may be well tolerated.

DIABETES MELLITUS

Hypercholesterolemia and hyperlipemia are common findings in diabetes only when the disease is uncontrolled. Since the use of insulin the serious prognosis of the patient with hyperlipemia has changed.²⁹ Blood chole-

terol and blood lipids in diabetics are now usually found within the normal range^{30, 31, 32, 33}

When cholesterol values of the blood over 400 mg per 100 c c are found, it usually indicates serious complications either present or imminent³⁴ Especially is this true in juvenile diabetes In a recent study of diabetic children by White and Hunt, 11 out of every 12 children with hypercholesterolemia showed either arteriosclerosis, retinitis, abscesses or lipemia retinalis

A low blood cholesterol in a diabetic, on the other hand, may be of grave significance³⁴ indicating some associated disease as, for example, tuberculosis Such patients do not live as long as the average diabetic

In diabetic acidosis high blood cholesterol values are found, the highest observed being 1420 mg per 100 c c with a total blood lipid content of 19.9 per cent Adequate treatment is followed by a rapid fall There appears to be no parallelism among the degree of acidosis, the blood sugar and the hypercholesterolemia

The cause of hypercholesterolemia in diabetes is not clear The marked rise in some cases of acidosis is thought by Man and Peters³⁵ to be due to hemoconcentration This, however, does not explain hypercholesterolemia in diabetes without acidosis In diabetes with arteriosclerosis there is an increased ester content,¹³ and there is evidence indicating that hypercholesterolemia and arteriosclerosis in diabetes may be influenced by the fat content of the diet⁵ In any event cholesterol deposits do occur as manifested by xanthomatosis, gall stones, and arteriosclerosis¹⁷ Adequate treatment will cause absorption of xanthomatous lesions, but whether early atheromatous lesions disappear is not known The aim of diabetic therapy now is the prevention of, or retardation of, arteriosclerotic changes Control of blood cholesterol may play an important rôle in accomplishing this⁶⁴

LIPOID NEPHROSIS

In this disease there is a marked deposition of fat in the kidneys and liver and to a lesser extent in other organs³⁶ Fat cells are found but are not prominent Blackman^{37, 38} has been able to produce lipoid nephrosis in rabbits by the injection of pneumococcus toxin He suggests that lipoids, and hence cholesterol, are liberated as the result of cellular destruction by the toxin rather than through any change in cholesterol metabolism Gainsborough³⁶ believes hypercholesterolemia in this disease is related to disturbed blood proteins Blackman's clinical observations strongly suggest a relationship between chronic pneumococcus infections and lipoid nephrosis The increase in blood cholesterol is due to an increase both in esters and free cholesterol The determination of blood cholesterol in this disease is helpful in diagnosis Curiously, according to Gainsborough and others,³⁶ the feeding of thyroid has little effect on lowering the blood cholesterol

THYROID DISEASE

Hyperthyroidism causes a drop in blood cholesterol while hypothyroidism brings about a marked increase^{10, 12, 39, 40, 41} Hypercholesterolemia in thyroid deficiency may be partly due to retention of cholesterol through diminished secretion in bile and lowered excretion in the intestinal tract In animals, experimental hypothyroidism causes a low cholesterol content in the bile With Wilkinson⁵¹ we have found the same to be true in cases of myxedema In hyperthyroidism, on the other hand, the cholesterol content of the bile has been normal or high It does not seem likely, however, that the total change in blood cholesterol in thyroid diseases can be accounted for by this finding alone As a rule in myxedema there is a decrease in esters and an increase in free cholesterol⁴⁰

That these variations in cholesterol are due to variations in thyroid activity and not due to variations in total body metabolism is shown by the fact that hypometabolism from other or unknown causes is usually not associated with the abnormally high blood cholesterol values found in myxedema⁴² Elevation of metabolism by dinitrophenol is not accompanied by a corresponding drop in blood cholesterol⁴³ as it is in hyperthyroidism Blood cholesterol determinations are, therefore, useful in differential diagnosis and in treatment of thyroid disease, especially hypothyroidism

The relationship of thyroid deficiency and hypercholesterolemia to atherosclerosis deserves mention Here again we have a condition long known to be favorable to the development of arteriosclerosis, both clinically and experimentally¹⁹ I have already spoken of the prevention of cholesterol atherosclerosis in rabbits by thyroid feeding Leary suggests that the possible waning secretion of the thyroid in later life may contribute to atheromatous changes¹⁵

HYPOPITUITARISM AND THE PITUITARY-THYROID RELATIONSHIP

It is well known that pituitary deficiency is accompanied by a low metabolic rate This has often been referred to as pituitary myxedema It has been suggested that this is the result of a deficiency of the anterior pituitary thyrotropic hormone which so profoundly influences the activity of the thyroid Clinically there are many differences between hypopituitarism and myxedema This led us to investigate the behavior of the blood cholesterol in hypopituitarism Since the basal metabolic rate in this condition is as low and often lower than in myxedema, we felt there should be a corresponding rise in blood cholesterol if the low metabolic rate was entirely due to thyroid deficiency Fourteen cases of hypopituitarism due to verified chromophobe tumors were studied from this point of view Of these 14 cases, only two showed a blood cholesterol of over 240 mg per 100 c c The average values are shown in the table

	Hyper- thyroid- ism	Acro- megaly	Non- hyper- thyroid	Myxe- dema	Hypo- pitu- itarism
No of cases	283	2	146	47	14
Blood cholesterol mg per cent (average)	134	156	179	355	209
B M R per cent (average)	+45	+19	+0	-26	-28

Thus clinical facts do not tally with experimental work. One must, therefore, assume that the low metabolism in hypopituitarism is not solely of thyroid origin and that myxedema is primarily a disease of the thyroid. As Evans⁴⁴ points out, myxedema may be compared to the menopause, since excess thyrotropic hormone of pituitary origin has been reported in myxedema, just as excess pituitary gonadotropic hormone is found at the menopause⁴⁵

BILIARY SYSTEM

Free cholesterol is found in the bile, and according to Schonheimer and Hrdina⁴⁶ it is in loose combination with bile acids, forming a complex which is capable of absorbing even greater quantities of cholesterol. Ingested cholesterol is thought to be absorbed through the excess of bile acids in this complex.

Time will not permit a discussion of the various opinions as to the mechanism of cholesterol deposits in the gall-bladder^{46, 47, 48, 49, 50}. It is sufficient to say that cholesterol is precipitated in the gall-bladder cavity and that such precipitation is probably the basis for cholesterol stone formation. Cholesterol deposits in the gall-bladder wall, the so-called cholesterosis of the gall-bladder, is accompanied by collections of fat cells. No adequate proof exists, however, that cholesterol is or is not secreted or absorbed by the gall-bladder mucosa. Wilkie⁴⁸ believes that hypercholesterolemia in dogs is followed by passage of cholesterol from the blood through the gall-bladder mucosa into the gall-bladder, and that if there is a low blood cholesterol, cholesterol will pass from the gall-bladder into the blood. Deductions from experimental work on dogs are hardly valid in view of the non-occurrence of gall stones in these animals. It would seem advisable to take advantage of long standing biliary fistulae in human subjects to throw more light upon this question. The rationale of dietary management with low cholesterol diets⁵ hinges upon this problem. It is doubtful that such passage actually takes place⁴⁶. It is conceivable, however, that cholesterosis of the gall-bladder wall might regress by diet in view of the similarity of the process to xanthomatous lesions. Of interest in connection with cholesterol gall stones or precipitated cholesterol in the gall-bladder cavity is the fact that feeding certain bile acids increases the bile acid secretion without increasing the cholesterol content of the bile⁵⁴. Such excess of bile acids might dissolve precipitated cholesterol or cholesterol stones, in much the

same manner as a cholesterol stone can be dissolved in a dog's gall-bladder where the cholesterol in the cholesterol-bile acid complex is exceedingly low.⁴⁶

The hypercholesterolemia of biliary obstruction often affords a useful diagnostic aid in the differential diagnosis of the cause of jaundice. The increase in the blood is in both free cholesterol and esters although the latter do not parallel the former. Any infection tends to counteract hypercholesterolemia, even when obstructive jaundice is present. In degenerative disease of the liver with marked jaundice the cholesterol is lowered, the chief drop being in the esters,⁵⁵ a very low or absent ester content being present in the rapidly fatal cases. That the hypercholesterolemia of obstructive jaundice is a purely mechanical effect is doubted by some.⁵⁶ The lowered cholesterol ester in degenerative disease is thought due to injury to the esterifying power of the liver cells,⁵⁷ although this view is not universally accepted.⁵⁶ Removal of the liver does not cause a drop in blood cholesterol ester content, in fact higher values are found.⁵⁹

HYPERCHOLESTEROLEMIA

Not infrequently a high blood cholesterol is found without evidence of the usual diseases of which it is characteristic. In our experience such findings have occasionally revealed unrecognized myxedema. Experience with total thyroidectomy for heart disease, as well as subtotal thyroidectomy for hyperthyroidism, has taught us that a high degree of thyroid deficiency may exist without the usual external manifestation of the condition. Thus a high blood cholesterol may be of clinical value, especially when metabolism tests are unsatisfactory, as for example in children.

On the other hand hypercholesterolemia is occasionally found with low metabolic rates, and while this must be considered presumptive evidence of thyroid deficiency, and as indication for a therapeutic trial of thyroid extract, the results of treatment do not always prove as satisfactory as they do in myxedema. We have found this combination in a few apparently healthy individuals under 40 years of age.

As a rule, hypercholesterolemia is found in individuals over 40 or 50 years of age.⁶⁻¹⁰ A proportion of these cases display undoubted arteriosclerosis. Early senility may simulate in some instances a mild thyroid deficiency, and at times it is difficult to decide which is present, if not both. Administration in the beginning of not more than 1 grain of desiccated thyroid U.S.P. daily may be well tolerated, often diminishing the blood cholesterol and producing clinical improvement. This, of course, should not be interpreted as always indicating thyroid deficiency.

Further studies should be made of these individuals with hypercholesterolemia. The cholesterol-ester ratio should be determined, the effect of thyroid, iodide and bile acid feeding investigated, and the bile and feces studied. The effect of cholesterol-free diets in hypercholesterolemia is worthy of further investigation.

In this paper we have not attempted to present the reports of various

investigators on minor variations of blood cholesterol. The effect of fever, sunlight, vitamins, adrenalin, liver and spleen ablation, anemia and pregnancy and many other measures have been studied. These variations rarely exceed the normal limits of blood cholesterol values which are wide. Differences in methods of determining blood cholesterol may give wide variations in results. Thus each laboratory should set its own standards for the normal range of total cholesterol, which is usually from 120 to 230 mg per 100 c c. At times this appears too wide a range, at other times it seems too narrow. It is safe to say, however, that a value of 300 mg per 100 c c or more must be considered above the average, but as to whether it is abnormal in all cases has as yet not been determined.

SUMMARY

1 Determination of blood cholesterol and cholesterol esters has clinical value.

2 Abnormal cholesterol deposits in the various tissues of the body bear a close resemblance, and on the whole are accompanied by higher blood cholesterol values. While the evidence suggests that inability of the organism to handle cholesterol properly is the cause of these lesions, it is still not entirely convincing from all standpoints. This theory must be considered a working hypothesis which further clinical investigation should prove or disprove.

BIBLIOGRAPHY

- 1 SCHONHEIMER, R. New contributions in sterol metabolism, *Science*, 1931, **lxiv**, 579-584.
- 2 BILLS, C. E. Physiology of sterols, including vitamin D, *Physiol Rev*, 1935, **xv**, 1-97.
- 3 SCHONHEIMER, R. Über eine Störung der Cholesterin-Ausscheidung (Ein Beitrag zur Kenntnis der Hypercholesterinämien), *Ztschr f klin Med*, 1933, **cxxiii**, 749-763.
- 4 ASCHOFF, L. *Arteriosclerosis* (Edited by COWDRY, E. V.), 1933, Macmillan Co, N. Y., p 1.
- 5 JOSLIN, E. P. Arteriosclerosis and diabetes, *Ann Clin Med*, 1927, **v**, 1061-1080.
- 6 ROSENTHAL, S. R. Studies in atherosclerosis, I and II, *Arch Path*, 1934, **xviii**, 473, III and IV, 660, V, 827-842.
- 7 MJASSNIKOW, A. L. Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, *Ztschr f klin Med*, 1925, **cii**, 65-78.
- 8 PARHON, C. J., and PARHON, M. L'Hypercholesterinémie de la vieillesse, *Comp rend Soc de biol*, 1923, **lxxviii**, 231.
- 9 GORDONOFF, T., and ZURUKZOGU, S. Cholesterin, Ergosterin, und Gefasssklerosen, *Schweiz med Wchnschr*, 1934, **lxiv**, 284-289.
- 10 HURWITZ, L. M. Blood cholesterol in thyroid disease: analysis of findings in toxic and non-toxic goiter before treatment, *Arch Int Med*, 1933, **li**, 22-32.
- 11 ANITSCHKOW, N., and CHALATOW, S. Über experimentelle Veränderungen der Kaninchen-Aorta bei Cholesterinsteatose, *Beitr z path Anat u z allg Path*, 1913, **lvi**, 379.
- 12 HURWITZ, L. M. Blood cholesterol in thyroid disease. II. Effect of treatment, *Arch Int Med*, 1933, **lii**, 86-95.
- 13 GIBBS, C. B. F., BUCKNER, E., and BLOOR, W. R. Cholesterol to cholesterol ester ratio in plasma of diabetics with advanced arteriosclerosis, *N. E. Jr Med*, 1933, **ccv**, 384-386.
- 14 ANITSCHKOW, N. Experimental cholesterol atherosclerosis, historical data (*in Arteriosclerosis by COWDRY, E. V.*), 1933, Macmillan Co, N. Y., p 281.

- 15 LEFAY, T Experimental atherosclerosis in rabbit compared with human (coronary) atherosclerosis, *Arch Path*, 1934, *vii*, 453-492
- 16 ANITSCHKOW, N Zur Aetiologie der Atherosclerose, *Virchow's Arch f path Anat*, 1924, *ccxlv*, 73-82
- 17 WARREN, S The pathology of diabetes mellitus, 1930, Lea and Febiger, Philadelphia, pp 119
- 18 WEISS, S, and MINOT, G R Nutrition in relation to arteriosclerosis (*in* *Arteriosclerosis* by COWDRY, E V), 1933, Macmillan Co, N Y, p 233
- 19 EISENBERG, PICK, PINFELS, BIRDI, ROSSIG, and MARFSCH Quoted by GORDONOFF and ZURUKZOGU⁹
- 20 LIEBIG, H Experimentelle Untersuchungen über die Jodwirkung auf die Atherosklerose, *Med Klin*, 1929, *xxv*, 1100
- 21 TURNER, K B Studies on prevention of cholesterol atherosclerosis in rabbits, effects of whole thyroid and of potassium iodide, *Jr Exper Med*, 1933, *lxiii*, 115-125
- 22 PARHON, C I, and ORNSTEIN, I Influence de la thyroxine sur la cholestérolémie et la lipémie, *Comp rend Soc de biol*, 1931, *cvm*, 303-304
- 23 LEVY, M, and LEVY, E Le traitement de l'hypercholestérolémie par la thyroxine, *Presse med*, 1932, *xl*, 240-242
- 24 STARLING, E H Principles of human physiology, 1930, Lea and Febiger, Philadelphia, p 42
- 25 TOLSTOI, E Effect of exclusive meat diet on chemical constituents of the blood, *Jr Biol Chem*, 1929, *lxviii*, 753-758
- 26 MCGAVACK, T H, and SHEPARDSON, H C Xanthoma accompanied by hypercholesterolemia, *ANN INT MED*, 1933, *vii*, 582-604
- 27 PLEWES, L W Nature and origin of xanthoma cell, *Arch Path*, 1934, *xxii*, 177-186
- 28 ANITSCHKOW, N Das Wesen und die Entstehung der Atherosclerose, *Ergebn d inn Med u Kinderh*, 1925, *xxviii*, 1-46
- 29 JOSLIN, E P, BLOOR, W R, and GRAV, H Lipoids in diabetes, *Jr Am Med Assoc*, 1917, *lxix*, 375
- 30 HUNT, H M Cholesterol in blood of diabetics treated at New England Deaconess Hospital, *N E Jr Med*, 1929, *cc*, 659-667
- 31 WHITE, P, and HUNT, H M Cholesterol of blood of diabetic children, *N E Jr Med*, 1930, *ccii*, 607-616
- 32 RABINOWITCH, I M Cholesterol content of blood plasma as index of progress in insulin treated diabetics, *Canad Med Assoc Jr*, 1927, *xxii*, 171-175
- 33 HUNT, H M Unpublished data
- 34 JOSLIN, E P What cholesterol means to me in the treatment of my diabetics, *Proc Interstate Postgrad Med Assemb N Am*, 1935 (In press)
- 35 MAN, E B, and PETERS, J P Lipoids of serum in diabetic acidosis, *Jr Clin Invest*, 1934, *xiii*, 237-261
- 36 GAINSBOROUGH, H A study of the so-called lipid nephrosis, *Quart Jr Med*, 1930, *xxiii*, 101
- 37 BLACKMAN, S S, JR Pneumococcal lipid nephrosis and relation between nephrosis and nephritis, clinical and anatomical studies, *Bull Johns Hopkins Hosp*, 1934, *lv*, 1-56
- 38 BLACKMAN, S S, JR Pneumococcal lipid nephrosis and relation between nephrosis and nephritis, experimental studies, *ibid*, *lv*, 85-130
- 39 MASON, R L, HUNT, H M, and HURATHAL, L M Blood cholesterol values in hyperthyroidism and hypothyroidism, their significance, *N E Jr Med*, 1930, *cciii*, 1273-1278
- 40 SCHWARZ, H, and TOPPER, A Cholesterol partitions of blood in myxedema, *Jr Pediat*, 1933, *iii*, 242-246
- 41 HURATHAL, L M Blood cholesterol and thyroid disease III Myxedema and hypercholesterolemia, *Arch Int Med*, 1934, *lvi*, 762-781

- 42 HURATHAL, L M Blood cholesterol and hypometabolism, Arch Int Med, 1934, lxi, 825-831
- 43 CUTTING, W C, RYTAND, D A, and TAINTER, M L Relationship between blood cholesterol and increased metabolism from dinitrophenol and thyroid, Jr Clin Invest, 1934, xiii, 547-552
- 44 EVANS, H M Growth hormone of anterior pituitary, Jr Am Med Assoc, 1935, civ, 1232-1237
- 45 ARON, M Le titrage des hormones prehypophysaires dans l'urine humaine, son interet dans l'exploration fonctionnelle des diverses glandes endocrines, Bull Acad de med, 1934, cxl, 273-275
- 46 SCHONHEIMER, R, and HRDINA, L Etiology of gall stones, chemical factors, Proc Soc Exper Biol and Med, 1931, xxviii, 944-945
- 47 ANDREWS, E, DOSTAL, L E, and HRDINA, L Etiology of gall stones, is cholesterol excreted by the gall-bladder mucosa? Arch Surg, 1933, xvi, 382-388
- 48 WILKIE, A L, and DOUBILET, H Passage of cholesterol through mucosa of gall-bladder, Arch Surg, 1933, xxvi, 110-121
- 49 WEFISER, H B, and GRAY, G R Mechanism of formation of pure cholesterol gall stones, Arch Path, 1934, vii, 1-9
- 50 RAVDIN, I S, RIEGEL, C, JOHNSTON, C G, and MORRISON, P J Studies in biliary tract disease, Jr Am Med Assoc, 1934, ciii, 1504-1509
- 51 WILKINSON, S A, HURATHAL, L M, and HUNT, H M Unpublished data
- 52 LEITES, S, and ISABOLINSKAJA, R Veranderungen in Gallenchemismus und Sekretion unter dem Einfluss des Thyroxins, Klin Wchnschr, 1933, xii, 149-150
- 53 TWISS, J R, and GREENE, C H Dietary and medical management of diseases of gall-bladder, Jr Am Med Assoc, 1933, ci, 1841-1847
- 54 WRIGHT, A, and WHIPPLE, G H Bile cholesterol fluctuations due to diet factors, bile salt, liver injury, and hemolysis, Jr Exper Med, 1934, lxx, 411-425
- 55 EPSTEIN, E Z Cholesterol of blood plasma in hepatic and biliary diseases, Arch Int Med, 1932, l, 203-222
- 56 GARDNER, J A, and GAINSBOROUGH, H Blood cholesterol studies in biliary and hepatic disease, Quart Jr Med, 1930, xxiii, 465-483
- 57 THANNHAUSER, S J, and SCHABER, H Über die Beziehungen des gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion, Klin Wchnschr, 1926, v, 252
- 58 SHEELING, M D, and VOSHELL, A F Xanthomatosis generalisata ossium report of a case simulating osteitis fibrosa cystica, Arch Int Med, 1933, lv, 592
- 59 THANNHAUSER, S J Die chemischen Leistungen der normalen Leber für die Vorgänge des intermediären Stoffwechsels, Klin Wchnschr, 1933, xi, 49-54
- 60 JOSLIN, E P Treatment of diabetes mellitus, 5th ed, 1935, Lea and Febiger, Philadelphia
- 61 MCGAVACK, T H, and SHEPARDSON, H C Xanthoma accompanied by hypercholesterolemia occurring in otherwise normal individual and in individual with acromegaly and diabetes, ANN INT MED, 1933, vii, 582-604
- 62 WILE, U J, ECKSTEIN, H C, and CURTIS, A C Lipid studies in xanthoma further contribution, Arch Dermat and Syph, 1929, xix, 35-51 Lipoid studies in xanthoma further contribution, *ibid*, xx, 489-500
- 63 ROWLAND, R S Anatomies of lipid metabolism, Oxford Medicine, iv, 2143
- 64 RABINOWITCH, I M Arteriosclerosis in diabetes, ANN INT MED, 1935, viii, 1436-1474

BLOOD CHOLESTEROL IN DISTURBANCES OF THE BASAL METABOLIC RATE

By LEMUEL C. MCGEE, PH D, M D, *Elkins, West Virginia*

BIOCHEMICAL studies in the metabolism of sterols have resulted in the accumulation of a vast amount of information concerning sterol content (usually recorded as cholesterol, either free or combined) of foodstuff, blood, tissues in general, and excretions. Little of this information can as yet be taken as fitting evidence in a hypothesis of the function of and intermediary metabolism of cholesterol. Clinical studies for a score of years have been appearing at an increasing rate until at present there are available blood cholesterol figures for the majority of diseases. Yet there is little diagnostic or prognostic information obtained from a knowledge of the blood cholesterol level that is not better obtained by other clinical studies of a given disease process.

The "sine qua non" of blood chemical studies for a clinician, i.e., a rapid, inexpensive, reasonably accurate method of estimation of a given constituent in a small volume of blood, appeared, in the case of cholesterol, in 1916. In that year, Bloor,¹ doyen of American biochemists in the field of fat metabolism, published a method for the extraction of lipoids and the precipitation of proteins in an alcohol-ether mixture. Subsequent to filtration and selective redissolving of the lipid fraction by chloroform, the estimation of cholesterol and related sterols is made by colorimetric application of the Liebermann-Burchard reaction. In the clinical studies which followed the publication of the method, blood cholesterol alterations were reported in epilepsy, cancer, primary and secondary anemias, obesity, the nephrotic syndrome, nephritis, arteriosclerosis, diabetes, hepatic disease, physical exercise, types of lipemia, growing children, syphilis, feeble-mindedness, lipid granulomatosis, infections such as scarlet fever and typhoid fever, toxemias of pregnancy, cholelithiasis, and, particularly in recent years, disease of the thyroid gland.

METHOD

For a period of two years the author made determinations of plasma cholesterol values in patients residing in Dallas County, Texas. The series, besides controls, comprises those patients having metabolic rate determinations in either Baylor University Dispensary or Parkland Hospital, and those drawn from private practice. The method used was that of Sackett,² a modification of the original Bloor¹ procedure. Its advantages, emphasized by the author, are found to be that (1) less alcohol and ether are required, (2) less time is required for the determination, and (3) less blood is required for cholesterol estimation. Determinations were made on

* Received for publication June 14, 1935

plasma which had been placed in a laboratory refrigerator for not more than 24 hours. It was demonstrated, however, that the total cholesterol values would remain constant for three or four days in plasma kept at low temperatures. All blood was drawn from fasting patients. The method determines "total cholesterol" and is to be distinguished from separate estimations for ester cholesterol and free cholesterol, a procedure involving the precipitation of the latter form by digitonin^{3,4}

RESULTS

In a control series of normal adults it is apparent that there are greater variations than the usual textbook figures for cholesterol values indicate. The majority of the controls were between 20 and 30 years of age. No sex difference appeared.

In 52 controls the values ranged from 150 to 228 mg for 100 c c with a mean reading of 198 and an average of 193 mg. It may be observed that 63.5 per cent of the controls had values between 181 and 210 mg.

TABLE I
The Spread of Cholesterol Values in Normal Adults

Mg	Mg	Mg	Mg	Mg	Mg	Mg
160	161-170	171-180	181-190	191-200	201-210	Above 210
1	6	4	8	9	16	7

From the group of patients who were seeking medical advice and whose metabolic rates were taken and found to be normal, we have arranged a good control group. No patient in this group had a diagnosis of thyroid disorder. There were few males in the group and a great majority of females were patients with symptoms of pelvic disease, menopausal disturbances or functional disorders of the nervous system. Fifty-eight patients, whose metabolic rate was neither greater than +10 nor less than -10, were selected at random. These showed a distribution of values that cover a somewhat wider range than the first control group. A table giving the sex, metabolic rate and diagnosis is appended.

The range was from 100 to 308 mg per 100 c c, with an average of 180 mg per 100 c c, from the comparatively greater number of cholesterol readings in the group of the lower level.

In the series studied there were 45 patients with a metabolic rate above +10. Five of these with rates above +50 had plasma cholesterol values of 182, 133, 168, 133 (the highest rate +89 and +91 on successive mornings) and 125 mg, respectively. Three of the values are undoubtedly in the abnormal group. Of five patients with metabolic rates between +40 and +50, the plasma cholesterol values were 162, 154, 188, 176, and 146 mg, respectively. From this group of 45 patients there could be selected 16 who had the history, symptoms and physical findings of undoubted thyrotoxicosis and who had been given such a clinical diagnosis.

TABLE II
Cholesterol Values in Patients with a Normal B M R

B M R	Race	Sex	Plasma Cholesterol	Clinical Diagnosis
-1	W	F	168 mg	Cardiac disease
+8	C	F	232 mg	Peptic ulcer
-5	W	F	178 mg	Ovarian deficiency
-7	W	F	186 mg	Chronic cholecystitis
+7	W	F	142 mg	Neurosis
-2	W	F	182 mg	Hypothyroid
+1	W	F	175 mg	Obesity
-7	W	M	176 mg	Varicose veins
-2	C	F	154 mg	Pregnancy
-9	W	F	154 mg	Chronic tonsillitis
-5	W	F	141 mg	Obesity Hunner's ulcer
-5	W	M	140 mg	Obesity
-4	W	F	134 mg	Simple goiter
+5	W	M	176 mg	Cachexia
-10	W	F	164 mg	Nephrosis
-2	C	F	196 mg	Menstrual disturbances
-8	C	F	182 mg	Salpingitis Migraine
+4	W	F	210 mg	Menopause syndrome
+2	W	F	163 mg	Chronic tonsillitis
-8	W	F	243 mg	Obesity
-3	W	F	120 mg	Sterility
-4	W	F	143 mg	Malnutrition
+5	C	F	136 mg	Obesity Varicose ulcers
-3	W	F	100 mg	Sinusitis
-10	W	F	130 mg	Pelvic infection
+6	C	M	164 mg	Arthritis
+6	W	F	140 mg	Pelvic infection
+2	C	F	143 mg	
-9	W	F	188 mg	Pyelitis
+5		F	168 mg	Fibroid uterus
-10	C	F	200 mg	Obesity Varicose ulcers
+6	W	F	203 mg	Obesity
-5	W	F	232 mg	Endocrine dyscrasia
0	C	F	170 mg	Salpingitis
-1	W	F	250 mg	Chronic bronchitis
+9	W	F	136 mg	Ovarian disorders
+2	W	F	144 mg	Ovarian deficiency
-5	C	F	219 mg	Salpingitis
+5	W	F	240 mg	Obesity
-6	W	F	237 mg	Salpingitis
+8	W	F	200 mg	Menopause
+6	C	F	150 mg	Salpingitis Obesity
-4	C	F	158 mg	Syphilis
-1	W	F	182 mg	Pelvic infection
+8	W	F	207 mg	Infected teeth
+7	W	F	166 mg	Obesity and C N S syphilis
-6	C	F	140 mg	Thyroid adenoma
-8	W	F	242 mg	Psychoneurosis
+3	C	F	154 mg	Salpingitis
-6	C	F	201 mg	Endocervicitis
-2	C	M	171 mg	Malnutrition
-2	C	F	211 mg	Pelvic infection
-3	C	F	170 mg	Rheumatic heart disease
-7	W	M	308 mg	Irritable colon
-2	W	M	230 mg	Arthritis
-2	C	F	222 mg	Obesity
-3	W	F	239 mg	
-7	W	M	280 mg	Chronic glomerulonephritis

TABLE III
Spread of Cholesterol Values in Patients with Normal B M R

Below 141 Mg	Mg 141-150	Mg 151-160	Mg 161-170	Mg 171-180	Mg 181-190	Mg 191-200	Mg 201-210	Mg 211-220	Above 220 Mg
9	6	4	8	5	5	3	4	1	7

TABLE IV
Patients with a Diagnosis of Hyperthyroidism

B M R	Race	Sex	Cholesterol
+89	C	F	133 mg
+91			
+37	W	F	120 mg
+13	C	M	116 mg
+50	W	F	176 mg
+51	W	F	125 mg
+18	W	F	130 mg
+68	W	F	182 mg
+49	W	M	162 mg
+87	W	M	133 mg
+42	W	F	154 mg
+57	W	F	168 mg
+38 }	W	F	280 mg
+31 }			285 mg
+36	W	F	143 mg
+40	W	F	150 mg
+43	C	F	158 mg
+40	C	M	146 mg
			153 mg

It will be seen from the table that the plasma cholesterol values do not parallel the metabolic rate. There is a fair tendency to low cholesterol values, however. The one exceptionally high cholesterol value (cholesterol 285 mg, B M R +38) deserves comment. The patient, Mrs E M, age 40, in 1932 became aware of weakness, moderate loss of weight, tachycardia and restlessness. For a period of 14 months she was treated by a physician for "heart disease." In bed during this treatment, she could gain a few pounds, felt well, and was not disturbed by tachycardia. But each time she was allowed out of bed (after a period of complete rest, sedatives, and the well-nigh omnipresent digitalis) her symptoms immediately returned. She changed physicians in 1933 at which time there was an exophthalmos, a diffuse thyroid enlargement, a heart rate of 128 with a regular rhythm and other signs of thyrotoxicosis. The first metabolic rate was +38. Two days later it was +31. The corresponding plasma cholesterol values were 280 mg and 285 mg. Five days after the subtotal thyroidectomy, the plasma cholesterol was 345 mg and the metabolic rate -2. Thirty-five days postoperatively, her metabolic rate was -20 and the plasma cholesterol 400 mg. Thyroid was given for a few weeks but was discontinued because she felt that as little as one half-grain daily made her nervous and conscious of her heart. Six months later the metabolic rate was +4, cholesterol 268 mg, and she had no complaints. Hence, while the expected shift in blood

cholesterol did occur with the change in the metabolic rate, the range was extremely well removed from our usual concept of a normal cholesterol value

Comprising the group of patients with a metabolic rate lower than -10 , there are 42 adults. Great variability and lack of consistency in plasma cholesterol values again occur as indicated in the general distribution.

TABLE V
The Spread of Cholesterol Values in Patients with B M R Lower than -10

Below 141 Mg	Mg 141-150	Mg 151-160	Mg 161-170	Mg 171-180	Mg 181-190	Mg 191-200	Mg 201-210	Mg 211-220	Above 220 Mg
6	2	5	5	7	2	4	3	1	7

There is a striking similarity between the distribution here and that of the group of patients with metabolic rates in the zone of -10 to $+10$. But a metabolic rate is a variable and unreliable device for classification. From this group there are 19 with symptoms and physical findings justifying a clinical diagnosis of myxedema or hypothyroidism. Such a diagnosis in these patients was not only justified by the recorded picture of the patient but also was proved by therapy with varying amounts of thyroid for a suitable period of time. A table of this group of 19 is given.

TABLE VI
Patients with a Clinical Diagnosis of Hypothyroidism

B M R	Race	Sex	Plasma Cholesterol
-14	W	M	120 mg
-19	W	F	154 mg
-24	W	F	133 mg
-21	C	F	226 mg
-24	W	F	166 mg
-25	C	M	180 mg
-26	W	F	168 mg
-15	W	F	168 mg
-29	W	M	144 mg
-33	W	F	147 mg
-18	W	F	133 mg
-36	W	F	182 mg
-20	W	F	294 mg
-18	W	F	226 mg
-14	W	F	176 mg
-31	W	F	222 mg
-26	W	F	273 mg
-25	W	F	176 mg
-18	W	F	162 mg

In this group suffering from hypothyroidism there are eight patients with a metabolic reading of -25 or lower. The plasma cholesterol values were determined to be 180, 168, 144, 147, 182, 222, 273, and 176 mg respectively. Only two can be said to be elevated suggestively.

From a study of these tables one cannot find any tendency toward an

inverse relationship between metabolic rate and blood cholesterol level. We are forced to the somewhat unexpected conclusion that the single plasma cholesterol determination gives no aid in making a diagnosis of thyroid disturbance in a given individual.

In passing over the material, we selected at random 20 patients of the group who had obesity as an outstanding physical finding.

TABLE VII
Cholesterol Values in Patients with Varying Degrees of Obesity

Weight	Plasma Cholesterol
184	188 mg
198	138 mg
179	219 mg
165	240 mg
210	150 mg
194	194 mg
153	118 mg
185	168 mg
182	266 mg
166	128 mg
170	154 mg
155	198 mg
173	120 mg
300	136 mg
183	130 mg
192	133 mg
212	164 mg
159	140 mg
175	200 mg
160	130 mg

There is no correlation here to attract our attention. Of the entire group of patients considered, only four had a positive blood Wassermann. The cholesterol values were 182, 158, 130, and 166 mg, respectively. A study of blood pressure with a view to the circulating cholesterol gave just as great a distribution of figures over the wide range as was found in the control series.

DISCUSSION

As early as 1922, Epstein and Lande⁵ called attention to an inverse relationship between blood cholesterol values and metabolic rates. Gardner and Gainsborough⁶ also noted such a relationship and refrained from attaching great significance to it because of the many exceptions to the findings in a few cases.

Hurxthal^{7, 8, 9, 10, 11} and co-workers have found cholesteremia in myxedema consistently, and a less regular but significantly low blood cholesterol in thyrotoxicosis. They have observed more than 500 patients in reaching this conclusion and feel that "cholesteremia in the absence of its few other common causes, points more specifically to thyroid deficiency than does the finding of a low basal metabolism." Goldbloom and Gottlieb,¹² in 1927, and Bronstein,¹³ in 1933, found an increase of blood cholesterol in cretins.

On the other hand, Levy,¹⁴ in a group of 10 patients with exophthalmic goiter, found six with a blood cholesterol value of more than 230 mg

Gilligan¹⁵ and collaborators observed cholesteremia in patients with low metabolisms and no clinical evidence of hypothyroidism. After thyroidectomy, these patients failed to keep a constant relationship between the basal metabolism and the blood cholesterol level.

Luden¹⁶ found the blood cholesterol in 35 cases of exophthalmic goiter to be within normal range, and Wade¹⁷ reported slightly increased values of blood cholesterol in patients with toxic goiter. Castex and Schteingart¹⁸ found no relationship between the basal metabolic rate and blood cholesterol values. In this connection it is of interest that Cutting¹⁹ and his co-workers, as well as Grant and Schube,²⁰ obtained no correlation whatever between blood cholesterol and metabolic elevations induced by dinitrophenol.

Several pertinent observations on blood cholesterol furnish some explanation to the finding of inconstant values in this or in other such series. Barreda²¹ evaluated the cholesterol tolerance test of Thannhauser and Burger in which five grams of cholesterol in olive oil are taken by mouth and the blood level determined four and 24 hours later. He obtained variable results in normal and diseased adults in that the blood cholesterol level often was lower four hours after ingesting cholesterol than before. Yet Wendt²² finds that the ingestion of olive oil alone increases the phosphatid and cholesterol level four hours after ingestion. Gardner and Gainsborough²³ and Bloor,²⁴ in reference to widely discrepant normal values, emphasize the taking of fasting blood samples. These authors are agreed that the level of the cholesterol content of human plasma, taken while fasting, can be raised or lowered by sufficiently prolonged feeding with diets of high or low sterol content. They are not agreed on the effect of a single meal on blood cholesterol (alimentary hypercholesterolemia) but the evidence is possibly more in favor of some degree of relationship generally between the amount of sterol ingested and the cholesterol level of the plasma during its immediate digestion.^{24, 25, 26}

Among published "normal" blood total cholesterol figures there are noteworthy variations. Bloor²⁷ found the plasma values for men to be from 170 mg. to 311 mg., with an average value of 220 mg., and the values for women to be from 210 mg. to 260 mg., with an average value of 240 mg. Most authors make no distinction according to sex. The normal, according to Klinert and Widal (quoted by Campbell²⁸), is 180 mg., while Campbell²⁸ suggests the range of 150 mg. to 200 mg. Milbradt,²⁹ comparing his own use of the Tschugaew reaction with other methods for cholesterol determination, finds the normal values extending from 103.6 mg. (Autenrieth) to 176.3 mg. Gardner and Gainsborough^{30, 23} find the normal fasting variance to be 131 mg. to 293 mg., with an average value of 200 mg. Hunt,³¹ with Bloor's¹ method, found a variance of from 118 mg. to 272 mg., with an average of 177 mg. cholesterol in normal blood. Denis³² had a range of 167 mg. to 255 mg., with an average of 220 mg. in his series of normal subjects. Epstein and Lande,⁵ using the Bloor¹ method soon after its publication, had normal values extending from 160 mg. to 200 mg., with most

of their values near the upper figure Boyd ⁴ found the normal total plasma cholesterol to be 162 mg as determined by his oxidative procedure

That one or more factors controlling the level of cholesterol in the normal blood plasma are beyond our present knowledge seems obvious. The variations in the majority of normal series are too great to allow unqualified interpretation of values in disease states. There is a concurrence in this view in the expressed conclusions of several workers thoroughly acquainted with blood cholesterol values. Gardner and Gainsborough ⁶ state that "in normal human plasma the variations of cholesterol content are so considerable that an average figure for the normal plasma cholesterol is devoid of meaning unless the normal limits of variation are taken into account." Hunt ³¹ and Bloor ²¹ have expressed similar opinions.

The action of a protein-precipitant is necessary if any fat solvent is to remove satisfactorily the cholesterol from plasma. This suggests the power of protein to retain cholesterol. The marked insolubility of cholesterol in water would make necessary such a function of protein or some other circulating constituent. Gardner and Gainsborough ³³ suggest that changes in the globulin-albumin ratio of blood may be related to the variations in sterol content of plasma under both normal and abnormal physiological conditions in man.

In seeking to understand disagreements between our findings and those indicating a more constant relationship between cholesterol metabolism and thyroid function a word might be said concerning the method. The author ³⁴ has used various blood cholesterol methods for several years and is acutely aware of their limitations. Periodically the standard solutions were checked. The time element and temperature of the solution affect appreciably the depth of blue. Bloch, ³⁵ in 1933, studied each step in the estimation of cholesterol by the Liebermann-Burchard color reaction, using the time of the maximum reaction, temperature, light, solvent, concentration of cholesterol, quantity of sulphuric acid, and quantity of acetic anhydride as variables in apparently well-controlled observations. He found that the color developed in 15 minutes by the Liebermann-Burchard reaction is due to only two-thirds of the cholesterol present but finds that this is constant. The optimum conditions which he determined are embodied in the Sackett ² procedure as used in these analyses.

Ninety per cent of the estimations were made by the author. The remaining analyses were made by a well-qualified senior medical student. It was found that an error of 5 to 8 per cent might appear in trials of the ¹¹ method made by using various known solutions of cholesterol and by adding, varying quantities to blood filtrates. All standard and unknown solutions were prepared in duplicate. The type of patient from whom blood was taken was rarely known to the author at the time of the estimation. Occasionally the two standards, for an unexplained reason, failed to check properly. In such instances the entire analysis of a fresh portion of the blood ¹²

Plasma reacted with phosphatidyl chloride. An electrically illuminated Klett colorimeter was used for the color determination.

in a location protected from the glare of extraneous light. We feel that there can be no question but what the great variations are due to an actual variation in the amount of blood sterol compounds reacting with acetic anhydride and sulphuric acid in chloroform solution.

Evidence is accumulating that body sterols are effective substances in minute amounts, that many closely related forms are to be found with slightly different degrees of saturation, or positions of chemical groups in the sterol nucleus, and with greatly different biological influences^{26, 26}. It is now apparent that a close chemical relationship exists between cholesterol and crystalline vitamin D, estrogenic and male sex hormones, cardiac glucosides, carcinogenic hydrocarbons, bile acids, etc.^{36, 37}. Then may not our plasma "cholesterol" readings be a titer of numerous circulating entities, each present in small and varying amounts in health and disease? Is it not likely that the sterol causing the cholesterol figure in plasma from a patient with carcinoma is entirely different from that compound producing the greater part of the color in an estimation from the plasma of a patient with myxedema?

The possibility of a geographic or climatic cause for the behavior of blood cholesterol cannot be dismissed since it has been difficult for workers to agree upon the normal figures for blood cholesterol using the same method in different parts of this country and in other countries.

CONCLUSIONS

1 The figures for fasting blood plasma cholesterol in 52 normal adults, by a reasonably well controlled laboratory procedure, cover a wide range. The lowest finding was 150 mg. and the highest 228 mg., with an average of 193 mg.

2 In 145 patients having the plasma cholesterol and metabolic rate determined concomitantly there was no suggestion of correlation between the two.

3 In a series of 45 of the above patients presenting a metabolic rate above the arbitrarily chosen figure of $+10$, the sought-for correlation was not apparent. In 16 individuals presenting the undoubted clinical picture of thyrotoxicosis, the cholesterol variation was not consistent for the group.

4 In a series of 42 patients of the total group a metabolic rate of less than -10 was found. Of these, 19 patients had well-defined evidence of a hypothyroid state. Here, too, there was no tendency for the plasma cholesterol value to reflect the condition of the patient.

5 The factors affecting the circulating cholesterol are too numerous for a single estimation to be of great significance in the diagnosis of disturbance of the thyroid function. That thyroid disease is accompanied by cholesterol changes is not to be doubted, and plasma cholesterol estimations may prove of aid in following the progress of an individual patient under treatment provided such estimations are made frequently.

In this study the author had the excellent cooperation of Dr E M Dunstan, Director of Clinics and Medical Director of Baylor University Hospital, Dr C Frank Brown, Chief of the Metabolism Clinic of Baylor University Medical Dispensary, as well as numerous senior students in collecting and preserving specimens of blood plasma

BIBLIOGRAPHY

- 1 BLOOR, W R Cholesterol in blood, Jr Biol Chem, 1916, xxiv, 227-231
- 2 SACKETT, G Modification of Bloor's method for determination of cholesterol in whole blood or blood serum, Jr Biol Chem, 1925, l, iv, 203-205
- 3 BLOOR, W R, and KNUDSON, A Determination of cholesterol in small amounts of blood, Jr Biol Chem, 1916, xxvii, 107-112
- 4 BOYD, E M A differential lipid analysis of blood plasma, Jr Biol Chem, 1933, ci, 323-336, 623-633
- 5 EPSTEIN, A A, and LANDE, H Studies on blood lipoids, the relation of cholesterol and protein deficiency to basal metabolism, Arch Int Med, 1922, xxx, 563-577
- 6 GARDNER, J A, and GAINSBOROUGH, H The relation of plasma cholesterol to basal metabolism, Brit Med Jr, 1928, ii, 935-937
- 7 MASON, R L, HURST, H M, and HURATHAL, L M Blood cholesterol values in hyperthyroidism and hypothyroidism their significance, New England Jr Med, 1930, cciii, 1273-1278
- 8 HURATHAL, L M Blood cholesterol in thyroid disease, effect of treatment, Arch Int. Med, 1933, lxi, 86-95
- 9 HURATHAL, L M Blood cholesterol in thyroid disease, Arch Int Med, 1933, li, 22-32
- 10 HURATHAL, L M Blood cholesterol and thyroid disease, myxedema and hypercholesterolemia, Arch Int Med, 1934, liii, 762-781
- 11 HURATHAL, L M Blood cholesterol and hypometabolism, etc, Arch Int Med, 1934, liii, 825-831
- 12 GOLDBLOOM, A, and GOTTLIEB, R The cholesterol content of the blood of infants and children, Canad Med Assoc Jr, 1927, xvi, 1333-1336
- 13 BRONSTEIN, I P Studies in cretinism and hypothyroidism in childhood I Blood cholesterol, Jr Am Med Assoc, 1933, c, 1661-1663
- 14 LEVY, M Les variations du cholesterol chez les basedowiens traites par la radiotherapie, Bull et mem Soc med d hôp de Paris, 1931, xlvii, 1844-1846
- 15 GILLIGAN, D R, VOLK, M C, DAVIS, D, and BLUMGART, H L Total ablation of normal thyroid, relationship between serum cholesterol values, etc, Arch Int Med, 1934, liv, 746-757
- 16 LUDFN, G Blood cholesterol in malignant disease and the effect of radium on the blood cholesterol, Collected Papers of the Mayo Clinic, 1918, v, 481-487
- 17 WADE, P A Clinical and experimental studies on calcium and cholesterol in relation to thyroid-parathyroid apparatus, Am Jr Med Sci, 1929, clxxvii, 790-816
- 18 CASTAÑ, M R, and SCHTEINGART, M La colesterinemia y la calcemia en los estados tiroideos, sus relaciones con el metabolismo basal, Soc Rev de Med Int (Buenos Aires,), 1925, i, 514-525
- 19 CUTTING, W C, RYLAND, D A, and TAINTER, M L Relationship between cholesterol and increased metabolism from dinitrophenol and thyroid, Jr Clin Invest, 1934, xiii, 547-552
- 20 GRANT, L F, and SCHUBE, P G Effect of alpha dinitrophenol 1-2-4 on man, Jr Lab and Clin Med, 1934, xx, 56-61
- 21 BARRIDA, J Über den diagnostischen Wert von Blutcholesterinbestimmungen nach peroraler Cholesterinbelastung, Klin Wchnschr, 1934, xiii, 290-292
- 22 WENDT, H Über das Verhalten der Phosphatide und des Cholesterins in Gesamtblut Plasma und Erythrocyten des gesunden Menschen nach Olivenölbelastung mit und ohne vorherige Phosphat darreichung, Biochem Ztschr, 1932, ccl, 212-219

- 23 GARDNER, J A, and GAINSBOROUGH, H Studies on the cholesterol content of normal human plasma, on the so-called alimentary hypercholesterolemia, *Biochem Jr*, 1928, *xxii*, 1048-1056
- 24 BLOOR, W R Diet and the blood lipids, *Jr Biol Chem*, 1932, *xcv*, 633-644
- 25 MAN, E B, and GILDEA, E F The effect of the ingestion of a large amount of fat and of a balanced meal on blood lipids of normal man, *Jr Biol Chem*, 1932-33, *xcix*, 61-69
- 26 MCCLURE, C W, and HUNTSINGER, M E The influence on blood lipids of single food-stuffs, *Jr Biol Chem*, 1928, *lxxvi*, 1-18
- 27 BLOOR, W R The distribution of the lipoids (fat) in human blood, *Jr Biol Chem*, 1916, *xxv*, 577-599
- 28 CAMPBELL, J M H Cholesterol in health and disease, *Quart Jr Med*, 1925, *xxiii*, 393-422
- 29 MILBRADT, W Zur Bestimmung von Cholesterin und Phosphatiden in kleinsten Gewebs- und Blutmengen, *Ztschr f physiol Chem*, 1933, *ccxvi*, 181-188
- 30 GARDNER, J A, and GAINSBOROUGH, H Studies on the cholesterol content of normal human plasma, *Biochem Jr*, 1929, *xxi*, 130-140
- 31 HUNT, H M Cholesterol in the blood of diabetic patients treated at the New England Deaconess Hospital, *New England Jr Med*, 1929, *ccv*, 659-667
- 32 DENIS, W Cholesterol in human blood under pathological conditions, *Jr Biol Chem*, 1917, *xxix*, 93-110
- 33 GARDNER, J A, and GAINSBOROUGH, H Studies on the cholesterol content of normal human plasma, the attraction of the proteins of plasma for sterols, *Biochem Jr*, 1927, *xxi*, 141-147
- 34 GRAY, H, and MCGEE, L C Cholesterol content of blood in epilepsy and in feeble-mindedness, *Arch Neurol and Psychiat*, 1932, *xxviii*, 357-369
- 35 BLOCH, A Das Cholesterin bei der Liebermann-Burchardschen Farbreaktion, *Biochem Ztschr*, 1933, *ccxvii*, 171-179
- 36 BLOOR, W R Fat metabolism, *Ann Rev Biochem*, 1933, *ii*, 147-164
- 37 ROSENHEIM, O, and KING, H Chemistry of the sterols, bile acids and other cyclic constituents of natural fats and oils, *Ann Rev Biochem*, 1934, *iii*, 87-110

THE USE OF HELIUM IN THE TREATMENT OF ASTHMA AND OBSTRUCTIVE LESIONS IN THE LARYNX AND TRACHEA

By ALVAN L. BARACH, M.D., F.A.C.P.,^{††} *New York, N. Y.*

INTRODUCTION

THE proposal of helium as a new therapeutic gas was based on the conception that its decreased specific gravity in relation to nitrogen would make a helium-oxygen mixture easier to breathe than a comparable nitrogen-oxygen mixture, such as occurs in air.¹ The molecular weight of helium being 4, and that of nitrogen 28, the substitution of 80 per cent helium for 80 per cent nitrogen, with the oxygen concentration 20 per cent, would provide a respirable gas mixture which would have 33 per cent of the density of air (table 1). Utilizing the physical formula F equals MA , where F

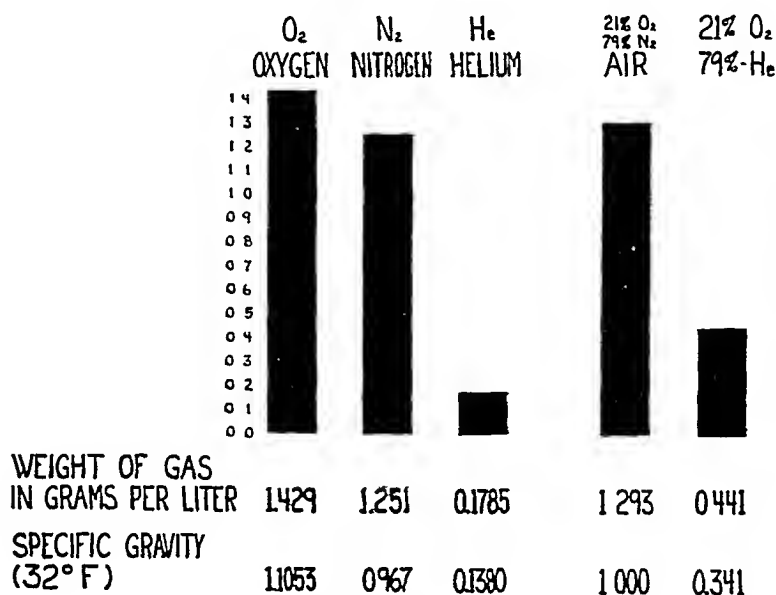


TABLE 1

Comparative weight of the respirable gases per liter

is Force, M is Mass and A is Acceleration, it may be said in general that the force necessary to transport a gas, other things being equal, is propor-

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.
 From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.
 † The author wishes to acknowledge assistance rendered to him by the United States Public Health Service, Bureau of Medicine and Surgery, United States Navy, The Linde Products Company, and the Helium Company, and to express his appreciation for their Governmental and other Government technical assistance of Louis Fekman, B. S.

tional to the density of the gas, and that in the case of an 80 per cent helium-20 per cent oxygen mixture, the force required would be one-third that necessary for movement of an 80 per cent nitrogen-20 per cent oxygen mixture. When passage of a gas through very fine orifices is considered, the rate of diffusion is proportional to the square root of the density, under these circumstances, the pressure required for this type of gas movement for an 80 per cent helium-20 per cent oxygen mixture would be approximately one-half that required for air.²

Wherever there is obstruction to the movement of air in the respiratory tract, an increased pressure is necessary to transport air to and from the lungs. In long-continued or severe obstruction, the increased back-pressure causes distention of the pulmonary alveoli and impairment in their function. The substitution of helium for nitrogen provides a respirable mixture which may be breathed with a pressure theoretically one-half to one-third that used for air. In previous reports^{1,2} it was shown that the force required for human subjects to breathe through narrow orifices was 35 to 50 per cent less when helium-oxygen mixtures were inhaled instead of air. This saving in respiratory effort has been made use of in patients with severe asthma and obstructive lesions in the larynx and trachea.

HISTORICAL

Helium was discovered in the sun in 1868 by Janssen and Lockyer³ by means of the spectroscope. Its existence on earth was demonstrated by Ramsay⁴ who obtained it from the mineral cleavite. It was later found to be a constituent of the atmosphere to the extent of one part in 200,000. Recently, it has been found to occur in certain natural gases. It has been used in dirigibles because of its buoyancy, having displaced hydrogen because it is free from explosive possibilities. In 1923, a patent was registered in the United States Patent Office by Charles Cooke⁵ for the use of helium with oxygen for divers, based on the fact that helium has a coefficient of solubility approximately half that of nitrogen, and because it is twice as diffusible. Sayers and Yant⁶ in 1926 decompressed animals from 10 atmospheres of helium-oxygen mixtures in from one-third to one-fourth the time necessary for nitrogen-oxygen mixtures and found no toxic effects from the use of helium under high pressures for short periods.⁷

In a series of papers Hershey⁷ reported that exclusion of rare gases from the atmosphere was not compatible with life, using small animals such as mice for experimental subjects. The author,⁸ during the past two years, carefully tested this hypothesis and found that animals lived apparently uninfluenced in atmospheres in which the rare gases were excluded for periods as long as 42 days. That helium was not itself harmful was next tested

* Elihu Thompson (Science, 1927, l.v, 36) called attention to correspondence with U. S. Bureau of Mines in which he suggested the use of helium for divers in 1919, theception having apparently arisen out of earlier experiments with hydrogen and formed in 1873.

A series of animals (mice) were kept in completely sealed chambers in which there was 79 per cent helium and 21 per cent oxygen. The chamber was cleaned twice a week, the technic of maintaining a constant percentage of the mixture has been described previously.⁸ The mice seemed uninfluenced by the substitution of helium for nitrogen for periods of two months, confirming previous evidence of its biologic inertness. Helium was then proposed as a therapeutic gas,¹ because its physical property of possessing the smallest specific gravity of any of the elements except hydrogen suggested that it could be moved more easily to and from the lungs in conditions where obstructive dyspnea was present. The highly explosive nature of hydrogen when mixed with oxygen excludes its clinical use.

METHODS

The administration of helium presents certain hazards that are more difficult to overcome than those encountered in the effective therapeutic use of oxygen. It is well known that oxygen therapy for years was employed in such small concentrations as to be of little or no value. The importance of knowing the concentration of oxygen inhaled by the patient has become generally recognized wherever high standards of medical practice are present, there are still to be found, however, instances of oxygen tent therapy in which the concentration of oxygen administered is not known. The patient may or may not be benefited under these haphazard practices but is not apt to be injured. In the use of helium mixed with oxygen, the danger of an inert gas displacing too much oxygen is constantly present, since an excess of helium will produce asphyxia. Careful oversight is also necessary to accomplish a rigid exclusion of nitrogen, for the beneficial effects of the inhalation of a lighter-than-air gas are lost when an inward leak of air enters the therapeutic atmosphere. Finally, the helium itself should be tested by an accurate helium analyzer to make sure that it is 97 to 99 per cent pure.

The present high cost of helium commercially makes it expedient to use it as economically as possible.* The apparatus employed for oxygen administration cannot be simply turned over for administration of helium and oxygen. A leak in an oxygen tent, for example, will create a loss of helium the n will speedily destroy the value of the procedure. The greater diffusion of helium over oxygen or air makes it necessary to employ special h material to prevent loss by diffusion through the tent fabric. Several h methods have been developed.

For relatively short periods of administration, such as one hour, a mask or mouthpiece apparatus has been used. A light rubber mask which fits tightly yet reasonably comfortably to the face is equipped with two one-inch outlets. One outlet is connected to the outside air by a rubber hose which

*Helium may be obtained from the Helium Company, Louisville, Kentucky. The Government has a large plant at Amarillo, Texas, which serves the Navy, the Army and other Government departments, but does not sell helium.

has an expiratory flutter valve at the terminal end. The other outlet is connected to an inspiratory flutter valve and then to a two-way metal valve by one-inch brass or mica tubing. The other end of the three-way valve is in turn connected to a Douglas bag, into which the gas mixture is admitted. A heater may be inserted three to four inches from the mask. When a heater is employed, a mouthpiece is used to inhale the heated helium-oxygen mixture, a thermometer being inserted just in front of the mouthpiece. The metal parts of the apparatus are insulated.

The purpose of using heated helium-oxygen mixtures is to decrease still further the density of the mixtures. Dry air between 200 and 250° F has been employed in some cases. In the accompanying table (table 1)

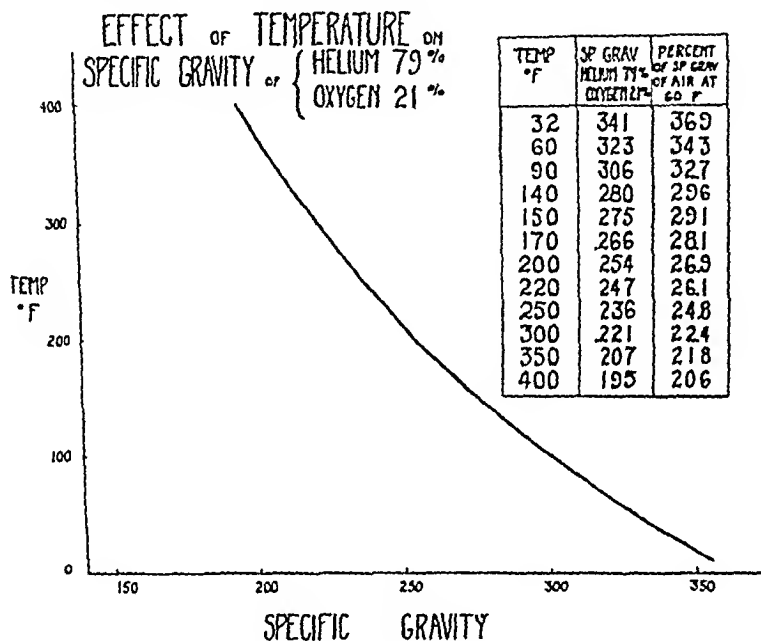


TABLE 2

the effect of increasing temperatures on the specific gravity of a gas is shown. The gas during respiration is gradually deprived of most of its heat and becomes saturated. However, the fact that the expired air may be 10 degrees higher than expired unheated air indicates that the in fourth heated gas is considerably less dense when it is passing through the bixic eff Helium-oxygen mixtures at room temperature have been used in most stances

Before treatment is begun, the Douglas bag is filled with helium and oxygen delivered from separate tanks through suitably calibrated gauges to make a mixture of 15 to 20 per cent oxygen and 85 to 80 per cent helium. As a check on the concentration finally attained, it is helpful to test the concentration of the combined gas as it enters the bag, or after it is filled. The inlet of the gas mixture is now changed so that it is run into the meta

tube that connects with the mask or mouthpiece, which is then attached to the patient. In many instances, 15 liters of helium and 3 liters of oxygen are thus admitted. As treatment is begun the two-way valve is turned so that the mixture from the Douglas bag is partly inhaled with the gas entering near the mouthpiece. When the bag is emptied, the patient is disconnected from the apparatus, the two-way valve closed so that the Douglas bag may again be filled, and the treatment begun again. The reason for switching the inlet of oxygen and helium from the bag reservoir to the mouthpiece connection is that a slight positive pressure is thereby developed which facilitates the inlet of the gas into the lungs.*

Experiments are in progress to develop a satisfactory method of re-using helium, by adding to a closed system the oxygen consumed by the patient. If valves are employed to circulate the gas through soda-lime, a positive pressure must be maintained to facilitate inspiration, since the patient with asthma finds it especially burdensome to develop additional inspiratory negative pressure to overcome the resistance in the tubing. A slight positive pressure in the system overcomes this resistance, which is then present during expiration. However, a slight increase in resistance to expiration is not uncomfortable and at times actually appears to facilitate the egress of the gas, perhaps by preventing further collapse of the bronchiole by high expiratory pressures. A motor-blower unit may be used to circulate the mixture through the system, provided also a slight positive

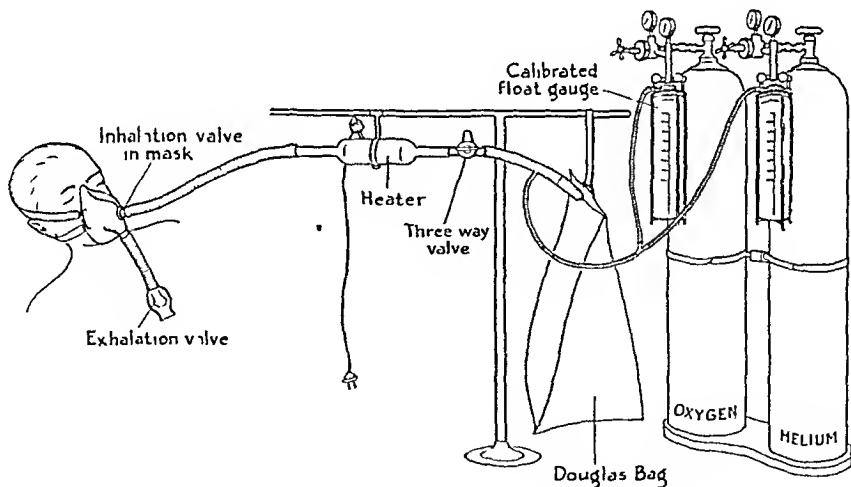


DIAGRAM 1 Apparatus for helium-oxygen inhalation

The inspiratory flutter valve should be slit open $\frac{3}{4}$ inch further to decrease resistance periods when large tidal volumes are inhaled. The complete apparatus may be obtained from the Oxygen Therapy Service Company, New York.

* The mask and the helium analyzer are made by the Mine Rescue Appliance Company, the infant gh, Pa.
 † The oxygen regulator is made by the Linde Air Products Company, New York.
 ‡ A high Forreger Company, New York, manufactures a calibrated water bottle.
 § A old man or is supplied by the Gruenberg Electric Company.
 ¶ The oxygen mixture Company is preparing mixtures of 20 per cent oxygen and 80 per cent helium to simplify the administration of the gas.

pressure is maintained (Diagram 2) A method of increasing pressure during inspiration and decreasing it during expiration, which will be synchronous with the patient's respiration, is being developed. In any of the methods employed to re-use the helium, the system must first be thoroughly

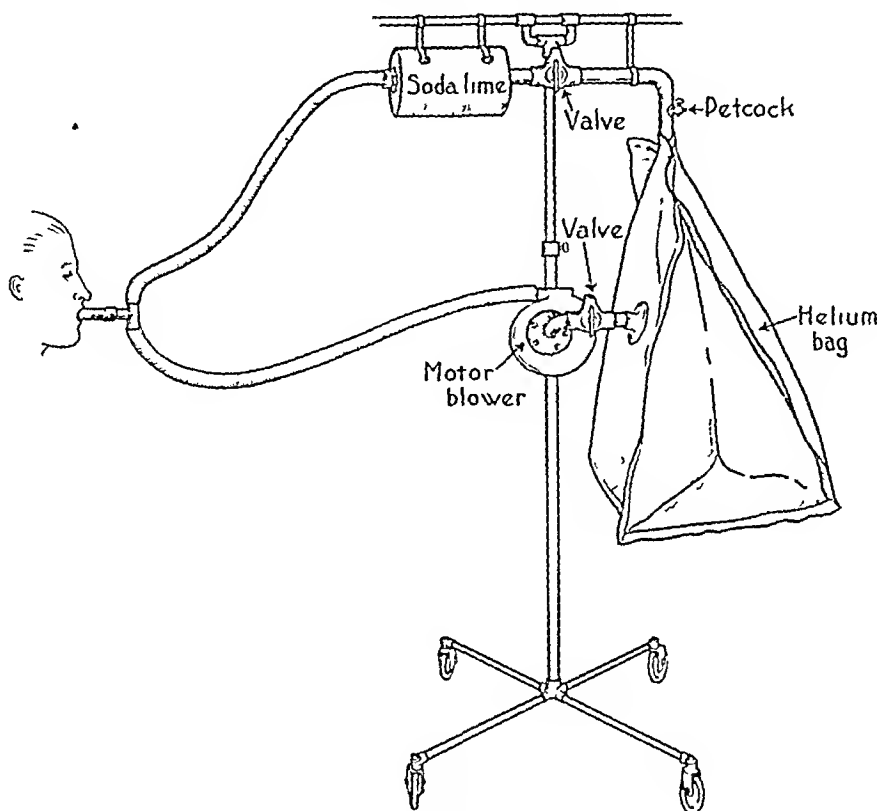


DIAGRAM 2

Helium rebreathing apparatus utilizing increased pressures

flushed with the gas mixture to remove all traces of nitrogen and a by-pass valve inserted by which the patient can breathe out the nitrogen of residual air. Oxygen is then admitted at a rate which corresponds to the patient's estimated basal metabolism. Repeated checks of the oxygen concentration are necessary to determine whether the inflow of oxygen is adequate to maintain the desired oxygen concentration. Tests of the helium concentration reveal the presence or absence of inward air leaks.

The oxygen tent has been modified to adapt it to the administration of helium with oxygen. The cooling, drying and ventilating are accomplished as originally recommended, by direct passage of the atmosphere over a bed of ice.¹⁰ The motor-blower unit must be leak-tight to helium. The canopy which encloses the patient is made out of special helium-proof balloon fabric. The material should be in one piece with an opening which makes a closure around the neck, or, particularly in infants, which covers the entire body. This opening is closed with zippers and the tent is filled with helium.

cloth folded over several times and clamped. Similar openings are present for administration of food and medicine. In both the adult and infant tents, a sleeve protrudes into the tent with a glove at the end, closed off from the inside atmosphere. The nurse may thus assist the patient without creating a leak. When treatment is commenced, in the tent used for adults, a bag is inflated within the tent, with the patient inside, with pure helium, while the remainder of the tent atmosphere is flushed out with a vigorous stream of pure oxygen. Air or nitrogen is thus reduced to a minimum. The bag is then opened within the tent. Adjustment of the desired concentration of helium and oxygen is accomplished by admission of these gases through calibrated gauges. If the canopy is built so that only the head of the patient is enclosed and contact is made around the neck, considerable saving of helium is effected.*

A helium testing apparatus has been developed by the Mine Rescue Appliance Company, based on the different diffusion propensities of air and helium. The helium concentration may be read off a dial within an accuracy of 0.5 per cent, in half a minute after the gas sample has been admitted into the diffusion chamber. A simpler, less expensive but less accurate apparatus may be constructed by calibrating the variable depression made on a water manometer by light and dense gases. If a constriction to the outflow of gas is produced, a considerable difference in water level will occur when a constant volume of air is delivered as compared to mixtures containing variable percentages of helium.

Since it is of obvious importance that the oxygen supply should never be interrupted, whatever method of administering helium and oxygen is used, two precautions have been adopted. The oxygen and helium gases are joined by a Y-tube immediately after their delivery from the gauge and passed thence into the tent by a *single* hose. The oxygen tank is connected by an arrangement developed by the Linde Air Products Company to a reserve tank which automatically delivers oxygen should anything happen to the one in use, such as the tank becoming empty or the valve inadvertently turned lower than the prescribed flow. The principle is simply that the reserve tank is set at a pressure just slightly lower than that at which oxygen is being delivered, and would therefore begin to function if the pressure in the first tank was for any reason decreased. An additional safeguard is an alarm which goes off when the oxygen flow stops.

The precautions enumerated and the determination of both oxygen and helium concentrations are necessary both for the effective use of this gas mixture as well as to safeguard the patient.†

* The adult tent was built by the Oxygen Therapy Service Company, New York, and the infant model by Mr. John Emerson, Boston, Mass.

† The effect of helium on the voice is characteristic and is a rough index of the presence of a high helium concentration. A high, quavering note is produced, resembling that of an old man or old woman. The lighter gas decreases the chest resonance. Inhalation of non-oxygen mixtures has given the voice an opposite quality, increasing chest resonance because of its greater density.

For those who plan to use helium therapeutically a few additional words on special problems involved in its administration may be helpful, especially since we are employing at the present writing methods which are being gradually improved.

In the simplest form of administration, the helium-oxygen mixture is inhaled partly from a Douglas bag and partly from the stream of the gas which enters near the mouthpiece. The importance of having the inhaled mixture enter near the mouthpiece instead of from the bag alone is that a slight increased pressure is thereby obtained which noticeably increases the comfort of the patient. The bag should be filled with the mixture before treatment is begun, from then on the desired flow, for example, 16 liters per minute of helium and 4 liters oxygen, is transferred to entrance near the mouthpiece. This flow would be necessary for only very high pulmonary ventilations, half as much would be used for low pulmonary ventilations. The exhaled atmosphere is wasted, passing into the air through the expiratory flutter valve.

For economic reasons it is highly desirable to re-use helium. A simple closed system in which the atmosphere would be blown through soda-lime presented certain difficulties. The first one was that leakage in the motor blower unit contaminated the atmosphere with nitrogen and lost helium more rapidly than oxygen because of its decreased density. It was found that if a pressure of 3 to 14 cm. of water was maintained in the system, the leaks would be outward and would therefore prevent entrance of nitrogen. This was done by insertion of a variable resistance in the tubing through which the exhaled air was passed. This increased pressure was found to be of decided value in increasing the velocity of the helium-oxygen mixture during inspiration without causing additional discomfort during expiration. (The reasons for this may be gathered from the body of this article and a forthcoming study on animal experiments.) Since it is known that the velocity of a gas is proportional to the square root of the increase in pressure, it became obvious that we could gain more by raising the pressure of the inhaled gas than we could by lightening its density through increasing its temperature, and we therefore have concentrated our attention on this phase of technic more recently.

By employing a Sturtevant motor-blower unit, the leakage in this closed system is slight, 4 liters of helium and 1 liter of oxygen per minute more than suffice to maintain the original atmosphere. Progress is being made in further reducing the leakage. In this apparatus, when the patient begins breathing through the mouthpiece, he first inhales air through the small valve mechanism to which the mouthpiece is attached. The Douglas bag is filled with the desired helium-oxygen mixture, usually 20 per cent oxygen, 80 per cent helium (at times 15 to 19 per cent oxygen, the remainder helium). A valve connected with the exhalation tubing is turned so that the patient's expired air goes into the atmosphere instead of into the closed system, in order that the 2 liters or more of the nitrogen of his residual air does not contaminate the helium-oxygen mixture being built up in the bag. The valve at the mouthpiece is next turned so that the patient inhales the helium-oxygen mixture instead of air. After he has taken 8 breaths, he has quite well washed the nitrogen out of his lungs and the valve referred to on the exhalation tubing side may now be turned so that he breathes into the closed system and the helium is re-used. The motor-blower unit is now turned on adding the increased pressure to inspiration. The reason that the turning on of the motor-blower unit has been delayed to this time is to prevent a large loss of helium which would otherwise have taken place when the patient was discharging the nitrogen of his residual air into the atmosphere.

When the bag has been filled, a flow of 4 liters of helium and 1 of oxygen maintains the helium concentration approximately constant. The oxygen consumption of the patient, 200 to 400 cc., may have to be compensated for by a very slight increase in the oxygen admitted, thus 1.2 instead of 1.0 cc. As we usually employ 17 per cent oxygen, the relatively small oxygen consumption by the patient makes little difference at the above flow, for after a little while the bag gets too full and a valve in the

nt past the bag must be opened and the gas mixture allowed to run into the air until e bag is somewhat reduced in size

If an absolutely leak-tight motor-blower unit were found, then it would be necessary merely to run in 200 to 400 c c of oxygen, depending on the oxygen consumption of the patient. It is obviously important to test the oxygen concentration of the gas entering the bag, which can be easily done in a minute by withdrawing a sample from a T-tube inserted in the rubber tubing which leads to the bag. The oxygen concentration in the closed system itself should also be tested to guard against leaks. Our practice is also to test the helium concentration by a densiometer, which reassures the operator of his technic in excluding nitrogen. It is essential to test the oxygen concentration to prevent undue accumulation of helium to asphyxial proportions. For that reason, the responsibility of administering this gas must rest with a physician, a technician may be employed to administer the gas under the physician's direction and responsibility, but it is not justifiable for a physician who does not comprehend the technic to request helium therapy from a purely technical service. The danger of death from asphyxiation is too real to be put under the control and management of technicians. With oxygen therapy the situation is obviously different inasmuch as no risk from asphyxia is present.

The author is at the moment experimenting with the Russ-Beach pump, which is light, and with the Roots-Connorsville blower. They possess the additional advantage of being capable of delivering the atmospheres at higher pressures, such as 0 to 13 cm of water, which enormously facilitate the entrance of the gas during inspiration but are high for expiration. An apparatus has been used in which the technician or nurse operates manually a valve by which the pressure is removed during exhalation and introduced during inspiration. An attempt is being made to accomplish this electrically by use of a photoelectric cell inserted near the patient's mouth. A small vane which moves toward the mouth during inspiration and away from the mouth during expiration interrupts a light from a photoelectric cell. The practicability of this latter apparatus has yet to be demonstrated, it is mentioned at this time for those individuals who actually plan to use helium.

The special importance of utilizing increased pressures during inspiration is to diminish the intrathoracic negative pressure which is high in obstructive dyspnea. In animal experiments the author has shown that edema of the lungs may occur in three hours, with circulatory failure, after continuous breathing through a resistance. The high intrapleural pressure not only acts like cupping the lungs but also sucks blood in the right heart and tends to prevent it from leaving the lungs, with resultant inadequate filling of the left ventricle. It has been shown that attacks of cardiac asthma are associated with a sudden increase in the volume of blood in the lungs (WEISS, STU ROBB, G P Jr Am Med Assoc, 1933, c, 1841). The administration of helium and oxygen under pressure not only facilitates pulmonary ventilation but also lessens the intrathoracic pressure, decreasing the accumulation of blood in the lungs, tending to relieve it or to ameliorate edema of the lungs and circulatory failure.

RESULTS

Asthma The rôle of helium in the treatment of asthma will be pre-hel'd by reciting the histories of four patients in whom its therapeutic effect is manifested and by illustrating through graphic records its effect on the phases of pulmonary ventilation.

The graphs in Case 1 were obtained by the patient breathing through a high resistance into a basal metabolism apparatus in which the CO₂ was re- old thl' her by the patient's respirations through soda-lime or by means gon-d e' caus' Low and high speed drums were used to record the qualitative

as well as the quantitative changes in pulmonary ventilation. In addition a measurement was taken which will be referred to as the pressure in the pulmonary air-way. The tube that leads off from the patient's mouth is tapped by a hard rubber hose that is in turn connected to a water manometer. As the patient breathes, especially when there is resistance external to the site where the breathing tube is tapped or when rapid forceful respiration are present, the pressure required to move the air in the respiratory system is communicated to the water manometer. The excursions of the water level are recorded on a moving drum by means of a delicate float which rides in the water of the distal arm of the manometer and which has attached to it a fine pen. The pressure readings thus obtained represent the pressure against which the respiratory musculature works and become thus an indirect index of respiratory effort. When the pulmonary air-way is entirely unobstructed and when respiration is proceeding slowly and quietly, there are recorded only very slight pressure differences. However, when rapid movement of air becomes necessary and particularly when a hindrance to the free passage of air develops in any part of the respiratory tract, the pressure in the pulmonary air-way is markedly increased and it is therefore under these circumstances that the decrease in the effort necessary to move a relatively light helium-oxygen gas becomes of clinical importance.

CASE REPORTS

Case 1 Male, age 26 years. Patient entered the Hospital on his sixth admission complaining of severe continuous asthma of 48 hours' duration. Attacks of asthma began two years ago. Since then, he had been admitted five times for asthma, complicated by either sinusitis, bronchitis or bronchopneumonia. Skin tests were negative. Treatment in addition to rest was mainly directed to the sinuses, although radical procedures were not undertaken. He left the Hospital a month previous to his present admission. At home, he was well for one week when his asthma returned with its accustomed severity, necessitating 10 injections of adrenalin daily for the remaining three weeks. During the 48 hours preceding his entrance to the Hospital, he suffered continuous asthma unrelieved by adrenalin.

On examination, he was seen to be a thin young man, acutely ill, breathing with great difficulty, inspiratory and expiratory, cyanotic and anxious. Lungs were filled with sibilant and sonorous râles, expiration was prolonged. Temperature 101.4°, pulse 110, respiration 30. Roentgenogram of lungs was negative. For the next 12 days, he suffered almost continuously from varying grades of asthma, adrenalin infrequently affording temporary periods of relief.

The Douglas bag apparatus, with a mouthpiece and with a mask, as described above, was used. At first, pure oxygen was administered, without alleviating the dyspnea, although his color improved. A mixture of 80 per cent helium and 20 per cent oxygen was then admitted into the system. After he had inhaled six breaths, relief became manifest and in two minutes he was asleep, the retraction in his chest muscles having almost completely disappeared. Most of the sibilant and sonorous râles in his chest were no longer present. Oxygen was gradually substituted for helium and when the concentration of oxygen got as high as 30 per cent, the dyspnea and râles returned. Administration of helium and oxygen again brought relief. At midnight, he was given 80 per cent helium and 20 per cent oxygen for one hour.

time He became relaxed, free from evident dyspnea, and slept restfully for six hours

In this patient, attacks of asthma were almost always preceded by severe cough-spells. Attempts to abort these attacks with the inhalation of helium and oxygen were unsuccessful. At the conclusion of these violent seizures, dyspneic asthmatic breathing continued which was then relieved by inhalation of helium-oxygen mixtures. The extent of relief varied, depending upon the type of bronchiolar obstruction he was suffering from at the time. When the larger bronchioles appeared to be constricting, as suggested by sonorous râles in predominance, relief might be estimated as between 90 and 100 per cent, if the fine bronchioles were constricting, as suggested by long-drawn-out piping and sibilant sounds, relief was estimated to be between 70 and 80 per cent.

The rest to his respiratory musculature was quickly apparent. His refractoriness to adrenalin gradually diminished, and the number of attacks lessened to two or three daily during the next two months. Helium, either through a mouthpiece or a mask, was given at intervals two to four times daily, for 15 minutes to 1 hour. Frequently, 85 per cent helium with 15 per cent oxygen was employed, since a greater degree of relief was obtained than with 80 per cent helium. The slight degree of anemia which the mixture induced seemed to be counter-balanced by the increased rate of penetration of the gas.

Therapeutic procedures aimed to cure the condition were not completely successful. Bacterial filtrates and vaccines were tried, residence in a dust-free room, oxygen chamber therapy, elimination diets, calcium and viosterol administration, nasal drainage, radical maxillary sinus drainage, roentgen-ray therapy of sinuses, splenectomy, bronchoscopic treatments, psychotherapy. For a period of one month, calcium and oxygen treatments were stopped. Asthma became gradually of the more continuous type, his adrenalin need increased to 5 and 6 injections daily. Helium-oxygen inhalations were instituted day and night for all continuous asthma—mild attacks and the asthma that persisted after severe seizures. The number of asthmatic attacks decreased to 2 or 3 daily, relieved by adrenalin. Continuous relief disappeared.

Inhalations of 15 to 20 per cent oxygen with 85 to 80 per cent helium were given minimal expiring the inspired air to between 200 and 250° F. Only dry gas can be used at these high temperatures. Although the mouthpiece felt somewhat hot when removed slightly from the teeth, the patient liked the sensation of the heated air in his chest and believed that he obtained more relief than from the mixture at a lower temperature. Furthermore, treatments were followed by expectoration of watery mucus. However, it was not possible to abort a severe attack. When an acute asthmatic seizure commenced and gradually increased, the patient received himself the helium-oxygen mixture for at times as long as 2 hours, with partial relief as long as he was inhaling it but with recurrence of severe asthma as soon as the mouthpiece was removed. The more continuous type of asthma responded much better to inhalation of helium-oxygen mixtures. Frequently, the patient asked for adrenalin because of pain in his ribs after he had had continuous asthma for a long period. This pain was completely relieved by breathing helium and oxygen without necessitating an injection of adrenalin. During the two months in which he was treated periodically, it became evident that refractoriness to adrenalin increased as he suffered more from continuous asthma, and that administration of helium-oxygen mixtures which relieved the continuous asthma was followed by disappearance of the refractoriness to adrenalin. This effect may be ascribed probably not only to rest of the respiratory musculature but also to the other integral parts of the respiratory system, the bronchial and bronchiolar musculature, the decreased alveolar distention, the end-ethetic nervous system, as well as the more conscious components of the respiratory system.

The following charts reveal some of the physiological effects of inhalation of helium and oxygen

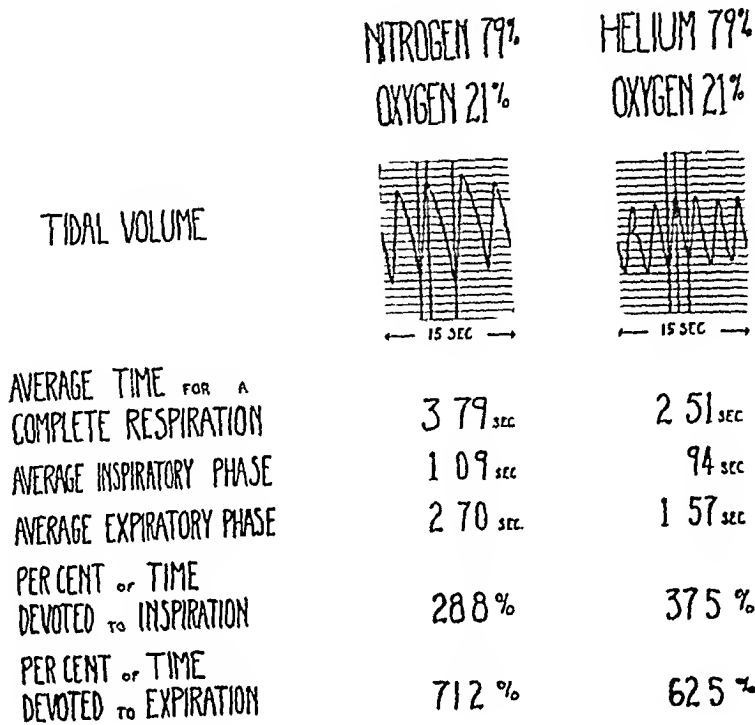


CHART 1

In the above chart (chart 1) a comparison of the respiratory cycle when the patient was breathing air and a helium-oxygen mixture was made during an attack of asthma. When air was breathed, the respiratory cycle was more prolonged and slow. The time occupied by expiration, both

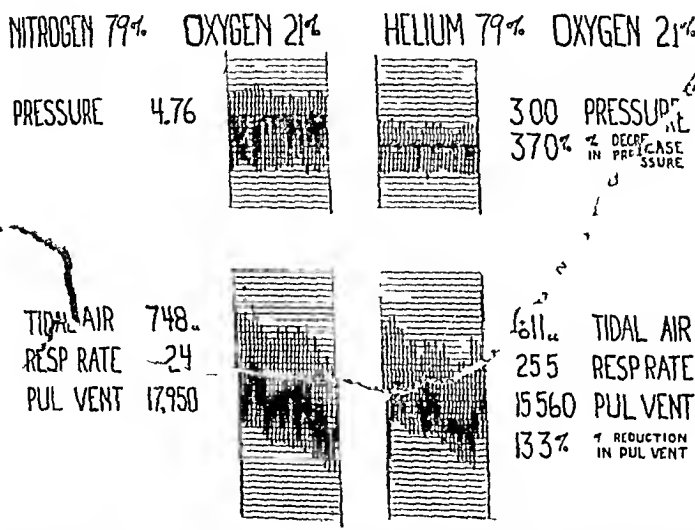


CHART 2 Patient in continuous asthmatic respiration Breathing helium-oxygen mixture pulmonary pressure reduced 37 per cent and pulmonary ventilation reduced 133 per cent

ely and relatively, was considerably less when the helium-oxygen mixture was inhaled. In addition, it can be observed that expiration, which is represented by the down-stroke of the graph, proceeds at a swifter pace at the very start of exhaling the helium-oxygen mixture, indicating a lessened resistance in which the alveoli are exposed to a distending expiratory pressure. In contrast, expiration takes place more slowly when air is breathed and with the maintenance of a higher pressure.

In the above chart (chart 2) comparison is made between the "pulmonary" pressure present when the patient breathed a helium-oxygen mixture and air. The decrease in this pressure is an index of the decreased resistance involved. The actual pressure differences recorded in the graph represent in large part the work performed against the resistance in the respiratory apparatus itself, but it affords an insight into the relative differences in pressure required to move air and the lighter gas in obstructions that are present in the interior of the respiratory tubal system, larynx, trachea, bronchi and bronchioles.

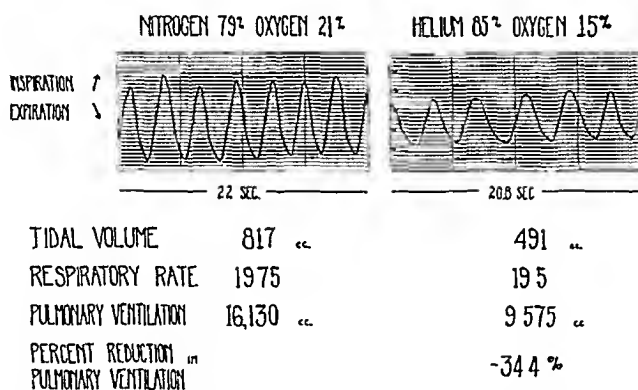


CHART 3 Patient in continuous asthmatic breathing. Increased rest period in each respiratory cycle and reduced pulmonary ventilation with helium-oxygen mixture.

In chart 3, the graph was obtained during a period of continuous asthmatic breathing. The decrease in pulmonary ventilation is very apparent. There can also be observed a difference in the quality of the respiratory cycle. During inhalation of air, the sharp acute angles at each respiratory cycle indicate the absence of a rest period, which is shown to be present during inhalation of helium and oxygen by the more rounded shape of the curve, with a pause at the end of expiration. The ceaseless activity of the respiratory musculature during chronic continuous asthma plays a role in the production of the fatigue which this type of patient suffers from and is probably involved along with other factors touched upon above in the development of refractoriness to adrenalin. In some attacks of acute severe asthma, although helium-oxygen inhalations decrease the need for increased pulmonary ventilations, the rest period is not produced, as is shown in the following

chart (chart 4) It is probably that this variation in response is dependent upon the size of the bronchioles that are most affected, the smaller the more difficult it becomes to give maximal relief

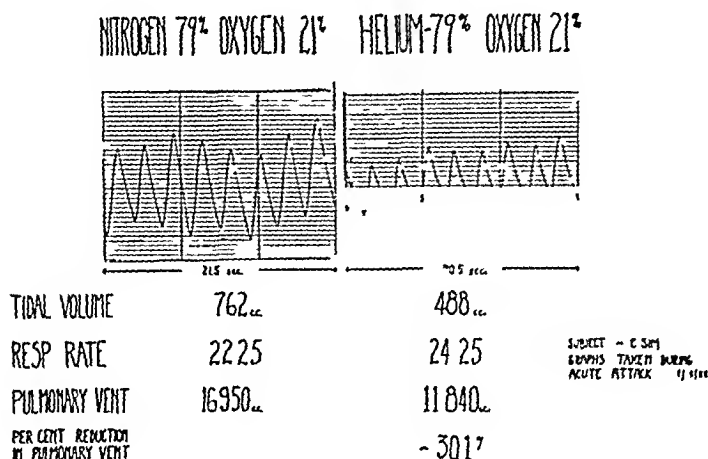


CHART 4

In this patient, the pulmonary ventilation during asthmatic seizure was increased almost three to four times his resting ventilation. This itself is of considerable interest and will be commented upon later. The effect of inhalation of helium-oxygen mixtures is almost always to decrease both the pulmonary ventilation and the tidal air.

Case 2 Male, age 22 years. **Past History** At the age of three, the patient's tuberculous glands removed from his neck. Following this, he developed tuberculosis and was in a tuberculosis sanatorium at six and again at fifteen. He had repeated attacks of head colds and bronchitis up to four years ago. **Present Illness** Two and a half months ago, the patient first developed asthmatic breathing and two weeks later he suffered a severe asthmatic attack which lasted three days. Since then, he has had asthma intermittently. On admission, he was seen to be a fairly well-developed man of 22, in typical asthmatic breathing. Lungs were filled with sibilant and sonorous râles, without dullness, expiration prolonged. He continued to wheeze for one week, when he contracted bronchitis with fever. The asthma then cleared for two weeks. During the seventh week, he caught a head cold which was improving when he suddenly began to wheeze. The asthmatic attack came progressively worse, unrelieved by adrenalin in repeated doses, or by morphine or atropine. He became cyanotic and was placed in an oxygen tent with 60 per cent oxygen. His color improved but asthmatic breathing persisted. His pulse gradually became weaker and at the end of 20 hours almost imperceptible. He became comatose. The breathing was in shallow gasps, the rate had declined to 15 times a minute. He appeared to be in imminent danger of respiratory failure. At 10:30 A.M., 3/20 of a gram, was given intramuscularly, with temporary increase in rate of respiration and marked accentuation of retraction signs in the neck muscles. Within five minutes, breathing again became slow, shallow and gasping.

A mixture of approximately 75 per cent helium and 20 per cent oxygen was maintained in the tent (the remainder water vapor and nitrogen), and the patient became conscious, retraction signs in the neck muscles improved and breathing became progressive. In two and a half hours

...athing helium-oxygen mixture
...duced 13.3 per cent

comfortable in the tent, there was no neck muscle retraction, breathing had increased to 20 per minute, the pulse was of fairly good quality and the tent was smaller. In about 15 seconds, the visible signs of asthma returned, accompanied by neck muscle retraction. However, the patient was rested, cheerful and out of danger. Subsequent attacks responded promptly to adrenalin. One week later, he returned home suffering from occasional attacks, and attempted to find work. Four weeks later, he was in good health, not inconvenienced appreciably by occasional attacks which promptly responded to adrenalin.

In this patient, the inhalation of a helium-oxygen mixture was followed by a marked improvement. It appeared to be an increase in pulmonary ventilation. He was too ill to permit getting a record of his tidal air, but the clinical impression was remarkable that he had an increased depth and an increased rate of respiration. Since he was inhaling the helium-oxygen gas. The respiratory muscles, which seemed on the verge of complete cessation of activity, were able to sustain such an extent after two and a half hours that the patient was able to breathe without discomfort the moderate degree of asthma which returned when the tent was removed.

Case 3. Female, age 40 years. Family History. One sister and a grandmother with asthma. Present Illness. Asthmatic attacks began two years ago. Since then, she has had numerous hospital admissions for severe asthma. Tonsillectomy, administration of bacilliferous filtrates and vaccines, drainage of sinuses and establishment of permanent openings, postural drainage and psychiatric interviews, were followed by no improvement. In the hospital, the asthmatic attacks always abated on residence in the oxygen tent for 10 days to three weeks, and twice in the filtered air room. After coming from the hospital for one week, she again returned with severe asthma. On admission, she was a thin, poorly nourished woman in severe asthmatic breathlessness. Lungs showed dullness and fine crepitant râles at right base and widespread throughout. Harsh and sonorous râles. Expiration was markedly prolonged. She was gradually relieved by adrenalin, 6 to 8 c.c. daily, oxygen tent with 50 to 60 per cent oxygen, and bromides and iodides. However, on the sixth week of residence in the tent, the attacks became steadily more frequent, ending in continuous asthma 8 hours. Adrenalin, large doses of nembutal and oxygen in the tent did not relieve her. She was aroused with difficulty and then was irrational, no doubt partly due to nembutal and bromides. Sibilant and sonorous râles persisted throughout the attack. She was taken out of the tent and a mask attached to her face. At first, she struggled against the mask but after 15 minutes of inhaling 18 to 20 per cent oxygen and 82 to 80 per cent helium, she was relaxed and accepted the treatment willingly. The relief of her dyspnea was noticeable and one hour later treatment was discontinued. Approximately 90 per cent of the râles had disappeared and she did not return that afternoon. She was both subjectively and objectively relieved of her asthma. An attack the following day was promptly relieved by adrenalin. She gradually improved, helium and oxygen being administered at intervals for three weeks. For two weeks she required no adrenalin, when wheezing and coughing recurred, necessitating for two additional weeks two to four injections of adrenalin. Attacks cleared up during the subsequent week and the patient left the hospital temporarily free from asthma.

The use of helium-oxygen mixtures in this patient was followed by a marked improvement in the relief of a persistent siege of continuous exhausting asthma and by

disappearance of refractoriness to adrenalin. The patient was a one to handle since she attributed her asthmatic attacks to the most antecedent treatment. The various procedures which were attempted all to be abandoned without a satisfactory trial for this reason.

Case 4 Male, age 52 years. Past History: Patient had had a chronic discharge for six years following a head cold. Present Illness: Asthmatic began five years ago. His first admission to this hospital was two years ago. He complained of almost steady asthma for the preceding three weeks. Allergic was negative. External ethmoidectomy and later frontal sinusectomy were performed. Following the latter procedure, asthmatic attacks were said to have become worse. Five days before admission, he went into status asthmaticus and entered hospital almost moribund. On physical examination, he was a middle-aged, thin and worn looking, obviously in extremis. His hands and feet were cold. Inspirations were very shallow and slightly labored. Lungs contained a few crackles and wheezes. There was slight dullness in the right anterior chest with depressed breath sounds. Heart was not enlarged, sounds were of very poor quality. Pulse was poor, rate 110, vessel wall sclerotic. W. B. C. 22,700, polymorphonuclear percentage 79. Patient seemed about to expire when he reached the ward. He was put into an oxygen tent in an oxygen concentration of 50 to 60 per cent. He was given morphine and atropine, and caffeine sodium benzoate 0.6 gram. The latter medication appeared to be followed by striking improvement in general condition, but status asthmaticus continued. On the following day, inhalations of helium 80 per cent oxygen 20 per cent were begun for periods of one hour. After the first inhalation, the patient became temporarily better, relaxed and relieved of asthma. Return of symptoms of the same severity was treated with adrenalin with little relief. A second period of inhalation of helium and oxygen for one hour was again followed by relaxation, sleep and freedom from asthma. Return of symptoms several hours later was again treated by adrenalin which this time was followed by disappearance of asthma. Patient was treated intermittently with helium-oxygen inhalations for the next two days, but following the disappearance of his refractoriness to adrenalin, patient preferred the injection to breathing through a mask. He progressively improved, leaving the ward three and a half weeks later, requiring at that time 18 injections of adrenalin in 24 hours.

In this patient, the administration of helium-oxygen mixtures for periods of one hour at a time was followed by interruption of a profoundly severe asthmatic state, temporary relief of asthma and disappearance of refractoriness to adrenalin.

B Obstructive Lesions in the Trachea and Larynx Two patients with carcinoma of the larynx had previously been subjected to tracheotomy. When the tube was closed, a test was made of the effect of inhalation of helium-oxygen mixture as contrasted to air. Relief was experienced in both cases, in one almost complete. A third patient with esophageal carcinoma was given helium-oxygen inhalations with marked relief of dyspnea and stridor, until an acute exacerbation of symptoms took place, necessitating tracheotomy. Measurement of the "pulmonary" pressure in the case of laryngeal carcinoma showed the same type of decreased pressure when the helium-oxygen mixture was breathed instead of air, as was shown in the first asthma patient reported in the previous section. The first case to be reported in detail is that of laryngeal edema in an infant.

5 Boy, age 4 months Patient had had a head cold with a cough for six days when suddenly his breathing became difficult and wheezy His subsequent examination revealed that he swallowed "something green" at 9 a m On examination the following afternoon, he was seen to be a fairly well developed boy of four months His breaths were accompanied by a sound which seemed to be produced near the larynx Lungs were negative except for occasional wheezing sounds Roentgen-ray examination showed a speck in the infra-glottic region Laryngoscopy was done, followed by bronchoscopy, with removal of a green tack from the esophagus On the following day, he became markedly dyspneic, with retraction of neck muscles, cyanosis and restlessness Administration of 90 per cent oxygen in a tent cleared the cyanosis but gave no relief to his dyspnea Helium was then added to a concentration of 80 per cent helium and 20 per cent oxygen concentration 20 per cent The boy became obviously more comfortable after a few minutes, with relief of dyspnea but with perceptible cyanosis Oxygen concentration was increased to 30 per cent, helium 70 per cent Color was then pink and cyanosis absent He was given codeine At 6 a m the following morning, he was removed from the tent and changed outside the tent Marked difficulty in breathing and restlessness returned After about six to eight coughing spells, between each one of which he had a free interval, a tracheotomy was done at 3 p m Patient was then comfortable and able to breathe during the following five days During the following five days, he had to be repeatedly bronchoscoped or aspirated to remove mucus plugging the trachea He developed bronchopneumonia during this period and died six days after tracheotomy At autopsy, a diffuse bronchopneumonia was found but no laryngeal obstruction or edema

In this case, the continuous inhalation of 70 per cent helium and 30 per cent oxygen relieved the obstructive dyspnea and cleared the cyanosis, whereas 90 per cent oxygen removed the cyanotic color but did not give any relief to the urgent obstructive dyspnea In this kind of lesion, residence in a helium-oxygen tent until the acute process in the larynx subsides would appear to be a rational procedure Laryngeal obstruction may occur as a result of trauma, or in the course of infectious diseases such as diphtheria, or as a consequence of tumors In any instance where a resolution of the obstruction may be expected, inhalation of helium-oxygen mixtures might be used to keep the patient over the period of obstruction

Female, age 6 weeks The patient suffered from stridor since birth and was admitted as an emergency On examination, she was a well-developed infant, gasping at each breath On inspiration, there was marked retraction of the suprasternal, intercostal, sub-xiphoid and subcostal spaces She became markedly cyanotic on crying Lungs were clear The administration of 90 to 100 per cent oxygen in the helium-oxygen tent removed most of the cyanosis but did not relieve the dyspnea When 68 per cent helium and 24 per cent oxygen were given, the dyspnea was very much relieved The retraction of the neck muscles disappeared but slight sub-xiphoid retraction was evident The helium employed at that time was put into the tanks as an emergency measure and was only 94 per cent pure * Obviously, even better results would have been secured if pure helium had then been available As it was, her respirations declined to 20 per minute in the tent where of helium and oxygen, she slept peacefully and could take her nourishment Two to 3 per cent of the atmosphere was water vapor The density of water vapor is less than that of air but much more than a helium-oxygen mixture Calcium chloride was added to ice to dry the air in some instances

without effort. When she was taken out of the tent, the respiratory rate a a
to 40 per minute, marked retraction of all the accessory muscles of respir most
came manifest, she became restless and unable to take her feedings. She npt deper
in the helium-oxygen atmosphere for eight days in the hope that the o naller
process might clear. No improvement in her condition when outside the
place and a tracheotomy was performed. The obstruction was found to be the pos
the bifurcation, its nature not discovered. Following the tracheotomy, she chatic
a bilateral pneumothorax with urgent dyspnea. This was relieved only was ago
oxygen concentration was kept above 90 per cent. At the end of 16 hours, lergic
reduced to 50 per cent, and in 3 days discontinued. The baby was well on were
after tracheotomy, except that repeated aspirations of the trachea were neave b
Three months later, she died suddenly. At autopsy, the tracheotomy tube wa enter
to have eroded a soft tumor in the tracheal wall and ruptured the innominate a e-aged

In this infant, the relief of dyspnea afforded by inhalation of a few cold
oxygen mixture was striking. Had the lesion been of the type that est with
have resolved, she could have been kept in the tent atmosphere for poor qu
definite period. The dyspnea that took place when the lungs were su nuclear
collapsed was not obstructive but rather dyspnea dependent upon He wa
oxygen-want. It was exceedingly interesting to observe the difr medica
pathogenesis of dyspnea in this child. In considering the dyspnea on, but s
the pneumothorax, it was instructive that the inhalation of 50 per cen
oxygen was without any discernible effect on the dyspnea, in fact, first inhal
not until concentrations above 90 per cent were administered that the dys Retur
was relieved. These high concentrations of oxygen are dangerous followed b
periods exceeding 12 to 16 hours daily and should generally be relingial hours
for concentrations below 60 per cent for the remainder of the 24 disappearance
Over long periods of time, such as two or more weeks, concentrat halations for
over 90 per cent oxygen should not be given, even when limited to s to adrenali
daily.* progressively
at that time 1

In these two patients, a slight increase in the oxygen concent
the helium mixture above 21 per cent (between 24 and 30 per mixtures for per
peared clinically more beneficial than lower oxygen concentrati profoundly se
only was the cyanosis relieved with the added oxygen but the pati arance of re
selves seemed less restless. An opposite response was obtained in
tients with severe chronic continuous asthma, in whom 17 per cent two patients
and 83 per cent helium were generally clinically superior to higher to tracheo
concentrations. It was observed that 21 per cent oxygen in helium wh inhalation
ministered to the infants with laryngeal and tracheal obstruction did no experie
come the marked cyanotic color, and lower oxygen concentrations def esophagea
increased the cyanosis and restlessness. However, in the patients relief of d
asthma, during continuous asthmatic respiration, there was only place, m

* In work to be published on the effect of high oxygen concentrations on white pressure
was shown that animals survived 12 hours a day pure oxygen, with 50 per cent oxy decreased p
remainder of the time, but that pathologic section of the lungs revealed in mar air, as was
organizing pneumonia. The use of concentrations of oxygen as high as 90 per cent The fi
not be discarded for emergency conditions, when it may be of critical importance infant
minister them, but their employment over long periods does not seem warranted in
experimental evidence

osis during the breathing of 21 per cent oxygen in helium, and there was a very slight and sometimes imperceptible increase in cyanosis when the oxygen concentration was still further reduced, such as to 17 or 18 per cent, an obvious increase in comfort. Obviously, the lower oxygen concentration was attempted in order to give as much helium and therefore as much physical relief as possible.

These differences in clinical response to the oxygen concentration in the helium mixture have been somewhat clarified by dog experiments which are to be reported separately. It appears likely that higher intrapleural negative pressures take place in laryngeal and tracheal obstruction than in asthma, and that with these markedly elevated negative pressures, there is a congestion and edema of the lungs, the lung being subjected to a kind of "dry cupping," which produces a more serious anoxemia and circulatory failure in laryngo-tracheal obstruction than is generally present in chronic continuous asthma, accounting for the greater benefit obtained by increased oxygen tension in these conditions. In general, the precise dosage of helium and oxygen will have to be estimated by gauging the degree to which anoxemia or respiratory fatigue is involved.

DISCUSSION OF RESULTS

Although four cases of asthma are insufficient for a final evaluation of the rôle of helium in the treatment of this disease, the beneficial effects which were obtained had sufficient uniformity to permit certain observations concerning the physiologic effects of this gas administered with oxygen.

When the patient was experiencing more or less continuous asthma relief was obtained by the inhalation of 80 to 85 per cent helium with 20 to 15 per cent oxygen. The character of the spasm appeared to determine whether the dyspnea was alleviated completely or partially. When the râles were predominantly of the thin, long-drawn-out, piping quality, the removal of the sensation of air-hunger was less marked than when more sonorous râles were present, suggesting involvement of the larger size bronchioles. Relief was felt after six to 10 breaths, as the nitrogen in the pulmonary residual air was replaced by helium. Objectively, the signs of overactivity of the accessory muscles of respiration, such as those in the neck, diminished, or, in some cases, disappeared. If the treatment was given for a short period, such as five minutes, return to respiration of air was followed in three to four breaths by recurrence of asthmatic breathing. When the inhalation of the helium-oxygen mixture was continued for an hour or more, the patient frequently, although not always, had a period of relief from asthma for six to eight hours. Furthermore, repeated inhalations for the more moderate, continuous asthma were apt to be followed by the disappearance of refractoriness to adrenalin and the clearing of asthma between attacks.

In three cases in which refractoriness to adrenalin became so marked

as to result in a serious or even grave condition, the inhalation of helium-oxygen gas produced a striking alteration of the clinical picture. The patients were either stuporous or comatose, the dyspnea suggested a decreased ventilation because it was slow and gasping, the pulse was rapid and poor in quality, cyanosis was marked without oxygen, retraction signs in the neck muscles were less marked than in an acute attack, the lung signs showed hyperinflation, piping sounds with long-drawn-out respirations distinctly less noisy than in an acute attack. The end-state of status asthmaticus suggested a type of respiratory failure in which the muscles of respiration were exhausted to the point of impending cessation of activity. Although in the early cases the severity of their condition precluded measurements of the tidal air, the pulmonary ventilation seemed diminished and anoxemia was present. The inhalation of helium-oxygen gas for one to two and a half hours was followed by complete disappearance of asthma, both subjectively and objectively, with return of consciousness and improvement of the pulse. In one case, recurrence of moderate asthma took place immediately, in the others, two and six hours after cessation of treatment. In these cases, the inhalation of helium-oxygen gas provided rest to the respiratory apparatus, an increased tidal air (clinically observed), and a state in which adrenalectomy was effective again in stopping bronchial spasm. The patients became ambulatory and were discharged from the ward.

Acute attacks of asthma were not aborted by helium-oxygen mixtures, nor, although their severity was diminished during the inhalation of the gas, were they sufficiently relieved to displace adrenalin when this drug was effective. The persistence of asthma of variable extent, in those instances when the patient did not receive complete or lasting relief from adrenalin, was the indication for the employment of helium-oxygen mixtures.

In the first patient, more or less continuous asthma dominated the clinical picture without, however, going over into a severe status asthmaticus. Graphic records during continuous asthma showed a marked increase in pulmonary ventilation, which was decreased when helium-oxygen gas was breathed. Furthermore, the ventilation was reduced, even when only

cent oxygen was inspired in the helium mixture. An interpretation of this clinically observed fact, that the inhalation of the lighter helium-oxygen mixture diminished the need for an increased pulmonary ventilation, leads to the suggestion that the primary cause for the sensation of air-hunger in this type of asthma is neither the presence of anoxemia nor CO_2 excess but rather an interference with the habitual rate of filling and emptying the lungs. The increased effort required to obtain the normal velocity of air delivered to and from the lungs appears to give the sensation of dyspnea. It represents an *equilibrium* that functions to a degree independently of respiratory gaseous exchange. Davies, Haldane and Priestley¹¹ have fully studied the respiratory response to resistance, and recognized that interference with the normal stimulation of the Hering-Breuer reflex elicited the feeling of air-hunger.

viously, the maintenance of a sufficient oxygen saturation of the blood and an adequate removal of CO_2 are basic impulses that determine function in health and disease, but in the patient with asthma in whom the normal ventilation is provided during the period of laryngeal spasm, these basic factors are not the initial cause of the sensation of dyspnea. In the first place, inhalation of pure oxygen removed the dyspnea without affecting the dyspnea. Secondly, inhalation of 15 per cent oxygen, which slightly increased the cyanosis, afforded relief when it was replaced with helium instead of nitrogen. That anoxemia is not the main cause of this type of dyspnea was evident also in the case of laryngeal spasm that had an increased pulmonary ventilation. The feeling of air-hunger was relieved when the concentration of oxygen was 24 per cent, and it was administered with helium instead of nitrogen. That CO_2 is not the cause of the increased ventilation may be reasonably inferred from the fact that CO_2 is 25 times as diffusible as oxygen (in water) and the pulmonary epithelium shows no inability to eliminate CO_2 in high concentrations if the needs of the body for oxygen are met. Richards and his author¹² have shown that CO_2 may be eliminated from passively congested, fibrotic or tuberculous lungs at a tension two or more times the usual concentration if the patient is provided with an adequate oxygen supply. Wiggins¹³ has reported tensions of CO_2 in the arterial blood of asthma patients which may be normal, lowered or elevated, depending on the type of asthmatic seizure. During periods of increased ventilation, the CO_2 is washed out.

The onset of air-hunger in patients with asthma and obstructive lesions of the larynx is, therefore, in part a reaction to an interference with the normal rate of filling and emptying the lungs. The sensation of the volume of air delivered to the lungs per breath is presumably interpreted through the Hering-Breuer reflex arc, which is operative in stimulating and terminating inspiration. The existence of an equilibrium designed to maintain a balance into the lungs of an accustomed volume of air at an accustomed rate is of considerable importance to recognize, for it appears to be reliable to a large extent for the strenuous efforts which the patient with asthma exerts in the attempt to maintain it. That a purely physical sensation of an adequate inlet of air into the lungs, separate from other chemical factors, is an essential factor in obstructive dyspnea is additionally confirmed by the exhaustion which the asthma patient develops by carrying on a pulmonary ventilation three to four times the normal for him, and by his response to the inhalation of a lighter gas of the same oxygen concentration. In the first case reported, the patient breathed an 80 per cent helium-20 per cent oxygen mixture during a period of continuous asthma and within two minutes showed a fall in pulmonary ventilation, relief of dyspnea and onset

of sleep. Calculations of Loewy and Zuntz have indicated that 1 mm. O_2 pressure difference suffices for the diffusion of 250 c.c. of O_2 per minute and 40 times this quantity of CO_2 . (Quoted by WIGGERS, C. The physiology of health and disease, 1934, Lea and Febiger, Philadelphia.)

of sleep When 100 per cent oxygen was then substituted for the oxygen mixture, dyspnea and increased ventilation recurred through the

That mixtures of oxygen and helium, when inhaled through the tree, may result in a swifter diffusion of oxygen through the epithelium, and that the relief experienced by the patient may be due to satisfaction of his oxygen-want must be considered Undoubtedly, the inertness of the gas makes it possible for the oxygen molecule in the presence of a high concentration of helium to travel at a high velocity, with less probability of being absorbed in the pulmonary air-way, therefore, more oxygen (as well as helium) molecules at the start of inspiration will travel through the small bronchi into the alveoli than when air is breathed The lessened pulmonary ventilation and air-hunger may conceivably be in part dependent on better oxygenation That this is not the predominant causal factor in the relief experienced is shown by the fact that under certain circumstances 85 per cent helium and 15 per cent oxygen will result in an alleviation of dyspnea, even though a slight increase in cyanosis can be observed A prolonged administration of 15 per cent oxygen with helium would be regarded unfavorably as a known consequence of anoxemia would ultimately aggravate the condition but at the onset of treatment it has appeared useful at times to start with a mixture, because a greater relief was felt by the patient Later the oxygen is increased to a 20 per cent concentration

Additional evidence for the existence of this kind of equilibrium is obtained by having a normal individual breathe through an orifice $\frac{1}{8}$ inch in diameter The sensation of air-hunger is quickly produced with an intact respiratory apparatus, without the production of anoxia or CO_2 accumulation, the inhalation of 15 per cent oxygen and 85 per cent helium, despite the production of a slight anoxemia, results in an immediate diminution of the sensation of air-hunger This response can safely be ascribed to the swifter and easier movement in and out of the lungs of the lighter gas

In the infant with obstruction in the trachea, the respiratory rate was 40 per minute and the clinical signs of respiratory obstruction were evident When the helium-oxygen mixture was inhaled in the tent, the rate fell to 20 per minute, with marked relief of dyspnea* That the presence or absence of anoxemia is also involved as a basic factor was revealed by the behavior of this infant as well as by that of the infant with laryngeal edema In both instances, a greater degree of comfort was produced when the oxygen was raised slightly above 21 per cent, in one case to 24 or 25 per cent oxygen and in the other to 28 to 30 per cent oxygen However, when the oxygen concentration was further increased, dyspnea of the obstructive type recurred An instructive occurrence was the behavior of the infant with tracheal obstruction after the development of pneumothorax The degree of anoxemia produced by involvement of both lungs was so

* This sequence was vividly revealed by motion pictures taken with the infant in the tent

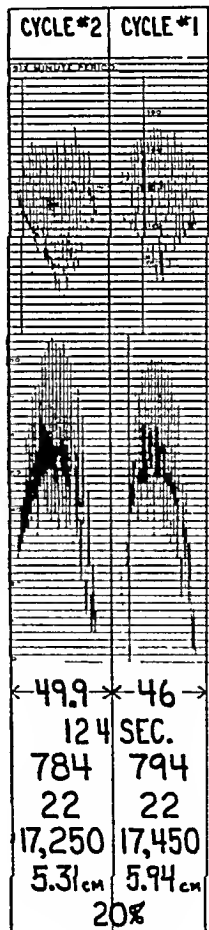
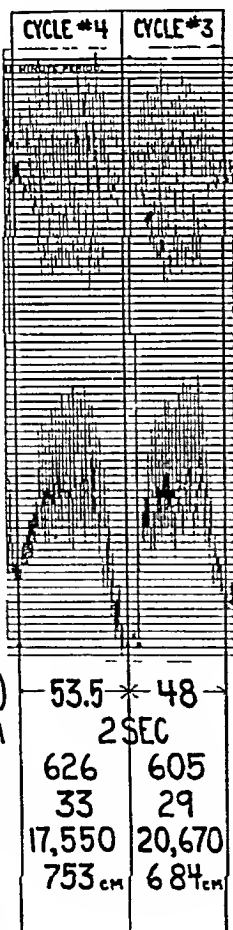
require for 16 hours the inhalation of 90 to 100 per cent oxygen to relief from dyspnea. That these high concentrations when continued over long periods are accompanied by the danger of pulmonary iron has been commented upon but it is of importance to recognize their value in such emergencies as arose in this case. Withdrawal of air from the pleural cavity was of great and immediate benefit. An additional estimation of the relief of dyspnea by the purely physical function of which independent of any chemical factor such as anoxemia or CO_2 excess, shown by the following record of a man with paroxysmal cardiac asthma. For our present purpose, it is unnecessary to review in detail his history. He was a man of 60 years, with pulmonary emphysema, chronic nephritis and myocardial fibrosis. His chief complaint was sudden, severe dyspnea which came on in attacks generally at night. Inspection of

NITROGEN 79% HELIUM 79%
OXYGEN 21% OXYGEN 21%

PRESSURE

TIDAL VOLUME

TIME OF CYCLE (SECONDS)
AVERAGE PERIOD OF APNOEA
AVERAGE TIDAL VOLUME
RESPIRATIONS PER CYCLE
PUL. VENT. PER CYCLE
PRESSURE
AVERAGE REDUCTION IN PRESSURE



5 Patient in severe Cheyne-Stokes dyspnea. Increased tidal volume during inhalation of helium-oxygen mixture with decrease in sensation of air-hunger.

these attacks revealed periodic respiration with a dyspneic phase of unusual severity. In the accompanying chart (chart 5), the graph of his pulmonary ventilation shows the very markedly increased tidal air (800 c.c.) which he breathed at the height of dyspnea. The patient could barely retain his mouthpiece because of the urgent sensation of air-hunger. When 10 per cent oxygen was inhaled, his breathing became regular, with immediate relief of dyspnea, which illustrates the chemical factor in the causation of this type of cardiac dyspnea.

When the patient inhaled a mixture of 80 per cent helium and 20 per cent oxygen, the dyspneic periods were characterized by an even greater tidal volume (up to 940 c.c.) than when he was breathing air and the apneic periods were correspondingly increased (chart 5). His sensation of air-hunger was diminished, notwithstanding the relatively great respiratory excursion, due to the ease with which these large volumes of light gas entered and left the lungs. During quiet breathing, no difference can be detected between the inhalation of air and helium-oxygen mixtures. When excessive volumes of air are brought into the chest, muscular effort is appreciable and under these circumstances the lighter gas mixtures require less effort on the part of the respiratory musculature, with a resulting decrease in the sensation of air-hunger. The consciousness of dyspnea is thus in part dependent on the nerve pathways which connect the muscles utilized in ventilating the lungs with the brain. Dyspnea is relieved, when the effort made by these muscles can be decreased either (1) by supplying a lighter respirable gas which physically decreases the amount of work done, or (2) by chemically reducing the amount of ventilatory work necessary, such as by decreasing the total oxygen consumption or by providing an increased oxygen concentration in the inhaled air.

The interpretation of the dyspneic state requires an understanding of the influences that bring it about. Harrison,¹⁴ in discussing the dyspnea evoked by mild exertion in cardiac states, says that it is not related to the partial pressures of the gases, the blood flow or the pH of the blood but is caused by disturbance of the proprioceptive reflexes arising in the lung. He emphasizes the factors of lung stiffening and lowered vital capacity. There appears to be little doubt that the sensation of dyspnea is experienced within the brain as a consequence of impulses sent along nerve pathways from the lungs and respiratory musculature, however, the evolution of the dyspneic state in a patient with congestive heart failure or with paroxysmal dyspnea is profoundly connected with the blood gases, oxygen and carbon dioxide, the blood flow and the composition of the blood. The increased pulmonary ventilation, which is a constant phenomenon in the dyspnea of heart disease, may be diminished in a number of ways, for example, by lowering the total oxygen consumption by the ablation¹⁵ or by inhaling oxygen-enriched atmospheres. The momentary first

* The longer periods of apnea present when helium-oxygen gas was breathed was probably due to the excessive washing out of CO₂ which the large tidal air volumes accomplished as well as maximal saturation of the hemoglobin in the arterial blood.

ly ventilation is reduced, the sensation of dyspnea is reduced. Since the basic purpose of ventilating the lungs is to provide oxygen to the arterial blood and the tissues, eliminating carbon dioxide at the same time, the basic cause of the dyspneic state must be sought for in a disturbance in this equilibrium, which does involve the blood gases, the blood flow and the pH of the tissues.* Richards and the author¹² have repeatedly observed the idea of heart failure relieved by the inhalation of 50 per cent oxygen, accompanied by a decrease in pulmonary ventilation, a slower pulse rate, an increased arterial oxygen saturation and an elevated arterial CO_2 content. Lowered oxygen tension in the blood or tissues admittedly does not itself cause the sensation of air-hunger, but it is responsible, together with the necessity of maintaining a suitable pH equilibrium, for much of the increase in pulmonary ventilation which characterizes the dyspnea of cardiac failure. This increase in pulmonary ventilation in the presence of disabled lungs stimulates the proprioceptive reflexes referred to. It has appeared necessary to us to limit the significance of the nervous reflex cause of dyspnea in heart disease in order to make clear its special importance in the experience of air-hunger in asthma and obstructive conditions in the respiratory tubal system.

SUMMARY

The specific gravity of helium being one-seventh that of nitrogen, a mixture of 80 per cent helium and 20 per cent oxygen has one-third the weight of a comparable volume of air. Since the pressure required to move a gas through the respiratory tract is in general proportional to its weight, it was assumed that a relatively light respirable gas could be breathed with less effort in clinical conditions in which difficulty in ventilating the lungs was present. In four patients with severe asthma, inhalation of helium-oxygen mixtures appeared to be of considerable benefit. When continuous asthma was present, subjective and objective relief were obtained. In three patients, in a severe or grave state of status asthmaticus and refractoriness to adrenalin, the attack was removed by inhalation of helium-oxygen mixtures. The acute attack of asthma was not aborted, and the relief obtained by inhalation of various mixtures of helium and oxygen was not sufficient to replace adrenalin when the latter was effective. The special value of helium-oxygen mixtures is in the treatment of asthma persisting after adrenalin and in status asthmaticus.

Graphic records of the quantitative and qualitative changes in pulmonary ventilation revealed the following consequences of inhalation of

The argument that the patient with congenital heart disease may have a low arterial oxygen tension without dyspnea does not take into account the admitted acclimatization mechanism by which individuals superficially adapt themselves to oxygen-want. The comparison may be made with the effect of morphine in addicts, in which large doses may not provoke sleep, but, on the other hand, large doses in unacclimatized individuals not only produce sleep but may indeed induce it. In both instances, the compensatory adjustments that develop are inadequate to the individual. The point involved is that acute oxygen-want acts as a chemical stimulus to breathing, perhaps largely through the carotid sinus reflex, and as such is frequently a factor in increasing the pulmonary ventilation of the dyspneic patient.

helium-oxygen mixtures on a patient with continuous asthma (1) do in pulmonary ventilation, (2) decrease in pulmonary pressure, (3) and absolute diminution in the length of expiration, and (4) increase period between respiratory cycles. The decreased pulmonary pressure and the swifter flow of gas during the early phase of expiration would tend to lessen the likelihood of alveolar distention and emphysema in patients who have much continuous asthma.

Severe obstructive dyspnea in two infants, one with laryngeal and other with tracheal obstruction, was relieved by inhalation of helium-oxygen mixtures. In one of these cases, the infant was comfortable in a helium-oxygen tent for eight days, but the congenital nature of the obstruction was such as to require tracheotomy ultimately. In conditions of laryngeal or tracheal obstruction in which there is a possibility of the obstruction coming up, the inhalation of helium-oxygen atmospheres may be useful by providing relief from a severe form of air-hunger and its consequent fatigue of the respiratory musculature.

The relief of dyspnea in patients suffering from various types of respiratory obstruction during the inhalation of helium-oxygen mixtures, makes evident the importance of an accustomed volume flow of gas to and from the lungs. This special equilibrium, i.e., the maintenance of a certain respiratory air flow, is regulated by proprioceptive reflexes from the lungs and the respiratory musculature. Disturbance in this equilibrium is the primary cause of the sensation of air hunger in this type of dyspnea, and emphysema may occur in severe cases as a secondary complicating factor.

BIBLIOGRAPHY

- 1 BARACH, A. L. Use of helium as new therapeutic gas, *Proc. Soc. Exper. Biol.* 1934, **XXXII**, 462-464.
- 2 BARACH, A. L. Treatment of heart failure by continuous oxygen therapy, *Anesth. and Analg.* 1935, **XLIV**, 79-88.
- 3 JANNSEN and LOCKYER. Quoted from *National Encyclopedia*, 1932, **v**, 222, P. 1.
- 4 RAMSAY, SIR W. The gases of the atmosphere, 3rd Ed., 1905, Macmillan and Co., London.
- 5 COOKE, C. U. S. Patent Office, 1923, Patent No. 1,473,337.
- 6 SAYERS, R. R., and YANT, W. P. Value of helium-oxygen atmosphere in diving caisson operations, *Anesth. and Analg.* 1926, **v**, 127-138.
- 7 HERSHEY, J. W. Physiological effects of oxygen atmospheres diluted by helium, *Trans. Kans. Acad. Sci.* 1929, **XXXII**, 51.
- 8 BARACH, A. L. Rare gases not essential to life, *Science*, 1934, **LXXX**, 593.
- 9 FORRER, A. Research on respiration of dry overheated air, *Arch. d. sc. biol.* 1931, **XXIV**, 1-10.
- 10 BARACH, A. L. New oxygen tent, *Jr. Am. Med. Assoc.* 1926, **LXXXVII**, 1213-1214. Importance of ventilation in oxygen tent and oxygen chamber therapy, *N. Y. State J. Med.* 1931, **XXXI**, 1263-1266.
- 11 DAVIES, H. W., HALDANE, J. S., and PRIESTLEY, J. G. Response to respiratory assistance, *Jr. Physiol.* 1919, **LIII**, 60.
- 12 BARACH, A. L., RICHARDS, D. W., MILHORAT, A. T., and LEVY, R. L. Effects of oxygen therapy on patients with congestive heart failure, *Proc. Soc. Exper. Biol. and Med.* 1929-30, **XXXVII**, 308.

BARACH, A L, and RICHARDS, D W, JR Effects of treatment with oxygen in cardiac failure, Arch Int Med, 1931, xlviii, 325-347

RICHARDS, D W, JR, and BARACH, A L Effects of oxygen treatment over long periods of time in patients with pulmonary fibrosis, Am Rev Tuberc, 1932, xxvi, 253-260

RICHARDS, D W, and BARACH, A L Oxygen therapy in pulmonary tuberculosis, Am Rev Tuberc, 1932, xxvi, 241

RICHARDS, D W, JR, and BARACH, A L Prolonged residence in high oxygen atmospheres, Quart Jr Med, 1934, iii, 437-466

13 MEAKINS, J C, and DAVIES, H W Respiratory function in disease, 1925, Oliver and Boyd, Edinburgh, page 196

14 HARRISON, T R Failure of the circulation, 1935, Williams and Wilkins, Baltimore, page 129

15 BLUMGART, H L, LEVINE, S A, and BERLIN, D D Congestive heart failure and angina pectoris, Arch Int Med, 1933, li, 866-877

SYMPTOMATIC PSYCHOSES IN PERNICIOUS ANEMIA *

By PAUL WM PREU, M D , and ARTHUR J GEIGER, M D ,
New Haven, Connecticut

ALTHOUGH it has been recognized for many years that mental disturbances are frequently seen in association with pernicious anemia, the inclusion of organic psychoses among the important manifestations of the disease is rarely emphasized and seems insufficiently appreciated. Some early authors, among them Barriett¹ and Lurie,² stressed the fact that certain of the psychoses seen in pernicious anemia should be grouped with the organic mental illnesses rather than with the functional or psychogenic psychoses. Warburg and Joergensen,³ in a comprehensive discussion of the subject in 1928, came to the same conclusion. Only one recent writer, Hackfield,⁴ considered that none of the psychoses seen in pernicious anemia were causally related to the physical disease.

The problem of psychoses accompanying pernicious anemia has apparently not been entirely ignored, but the careful differentiation of those psychoses which are an integral part of the organic disease from those which are merely coincidental has not received its due consideration. Many writers, including Smith,⁵ Smithburn and Zervas,⁶ Ahrens,⁷ Grinker,⁸ and Goldhamer and collaborators,⁹ have omitted any discussion of the psychiatric differential diagnosis entirely, and they have either merely enumerated the various mental symptoms observed, or they have grouped all the psychiatric disturbances under the general heading of "cerebral" or "psychic" symptoms.

The designation of symptomatic psychosis naturally implies an underlying physical disease, and such a psychosis is regarded as dependent upon an organic disturbance of cerebral function. The diagnosis of symptomatic psychosis is seldom difficult if its cardinal features are kept in mind. Kahn,¹⁰ in a recent discussion of psychoses accompanying physical disease, restated that a disturbance of consciousness is the distinguishing feature of the psychiatric syndrome which has variously been termed symptomatic psychosis, toxic psychosis, delirium, or acute organic psychosis. The author discussed the complex clinical picture in some detail and pointed out how the primary disturbance of consciousness leads to confusion, disorientation, and defects in perception, registration and memory. The patient experiencing the disordered state of cerebral function may become irritable, depressed, delusional, or excited. It is emphasized that the disturbance of consciousness, manifested clinically in diverse ways, is the pathognomonic feature

* Received for publication August 30, 1935

From the Departments of Psychiatry and Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

It is not improbable that the symptomatic psychoses arising in pernicious anemia have been insufficiently recognized because, on the one hand, few internists have applied the established diagnostic criteria of psychiatry to the mental symptoms they have observed and, on the other hand, the psychiatrists have too often inadequately identified and described the associated anemia

We wish to report three recently studied cases of classical Addisonian pernicious anemia personally observed by us in which the psychoses seem clearly to bear a symptomatic relationship to the deficiency disease

CASE REPORTS

Case 1 History C C, a white American spinster, aged 50, was admitted to the Psychiatric Clinic on July 8, 1933 with a referring diagnosis of tabo-paresis, made by a neuro-psychiatrist in private practice

The ancestral stock, Irish and German, was made up of typically pyknic and extroverted individuals. The family had been remarkably long lived. The patient's father had been a heavy drinker and subject to wide swings of mood. He had been excessively irritable and had entertained unfounded suspicions and jealousies concerning his wife. One of the patient's sisters was moderately addicted to alcohol, and another was an inhibited "old-maidish" person. A third sister, aged 48, had been in a state hospital for the past 13 years with a diagnosis of psychosis with constitutional psychopathic inferiority.

The family had always been poor and had lived much within itself as a fairly harmonious group. Outside, religious, social or sexual interests were few.

The patient had been headstrong as a child and had left school at her own volition at the age of 12 in order to go to work. She had always been intellectually sluggish and disinterested, was deficient in common sense and dexterity, and displayed but little energy in her work and activities. She cultivated female friendships readily, but they were always shallow. Her family regarded her as a simple, submissive, and childish person. Although she manifested minor periodic mood swings she was not given to brooding, exhibited no extraordinary emotional outbursts, expressed no feelings of inferiority or anxiety, and voiced no delusions or hallucinations. At 46 she passed through the menopause without any obvious physical or mental disturbances.

The present illness developed insidiously. During the year previous to admission the patient complained frequently of increasing fatigability. Progressive weakness ultimately rendered her incapable of assisting with housework, and eventually she could not walk the few blocks to attend church. She became forgetful, irritable, and nervous. Awkwardness in walking troubled her, and she was apt to fall if she stooped over, although no spasticity was observed. An exacerbation of all her symptoms followed the emotional disturbance occasioned by the sudden death of a brother three months before admission, and subsequently she became an invalid and made little attempt to help herself. The mental symptoms likewise progressed during the three months preceding admission. There was no weeping or obvious emotional depression, but she would sit staring ahead silently for long periods of time and seemed incapable of thinking clearly. At times her family thought her confused. No hallucinations or delusions were expressed. For a few days before admission she was incontinent of urine and feces, and complained of pain in her feet.

During the year of illness the patient had lost 25 pounds in weight, although her appetite had continued good. There had been no complaint of glossitis, stomatitis, or gastrointestinal disturbances, and no pains or paresthesias in the extremities. Neither had there been dyspnea or palpitation.

Physical Examination The patient was poorly nourished, the skin had an icteric tint, and the mucosae were slightly pale. The pupils reacted normally to light and on accommodation. There was only slight papillary atrophy at the tongue margins. The teeth were unclean and extensively carious. The heart, lungs and abdomen were normal, neither liver nor spleen was felt. Neurological examination revealed sluggish superficial abdominal reflexes, questionable extensor responses on plantar stimulation, and absence of knee and ankle jerks. The deep tendon reflexes in the arms were normal, and the cranial nerves were intact. Sensory and cerebellar function could not be tested because of lack of cooperation. The vital signs were normal; the blood pressure was 110 systolic and 85 diastolic.

Laboratory Findings The red blood cells numbered 3,200,000 per cubic millimeter, and the hemoglobin was 10.9 grams (70 per cent Sahli). The white cell count was 10,500, with 85 per cent polymorphonuclear cells. There was marked anisocytosis and poikilocytosis of the red cells, with a notable excess of macrocytes. Actual measurement of 300 red cells after the method of Price-Jones, indicated a mean diameter of 9.5 micra, with a range of cell diameters between 4 and 13 micra. Platelets did not seem diminished in numbers in the blood smear. Gastric analysis showed no free hydrochloric acid even after the injection of 1 mg of histamine. The stools were normal on several examinations, showing neither macroscopic nor occult blood, and giving no evidence of parasites or ova. The urine was normal. Complete fluoroscopic examination of the gastrointestinal tract disclosed no organic pathologic lesion. The blood Kahn test was negative, and the non-protein nitrogen was 58 milligrams per cent. Examination of the cerebrospinal fluid was negative.

Mental Status On admission the patient lay quietly in bed. No abnormalities of the motor status were noticeable. Speech was normal at the sensorimotor level. She was apparently confused. From time to time she asked the nurse for a bed pan but when it was brought she acted as if she did not know that it was there and appeared bewildered when questioned about it. She talked in a rather childish, colorless way. She was correctly oriented for place and person, but disoriented for time. When asked what month it was, she said, "June ain't it? I can't think what month anyhow." The stream of speech was slow, but showed no intrinsic peculiarity. Her content of thought was poorly verbalized, but no delusions or hallucinations were expressed. Her attention was poor and fluctuated, but distractibility was not noteworthy. Her emotional tone was flat and colorless, although depression was not manifest. During the physical examination, however, she rolled around, groaned, and acted in a negativistic fashion. Memory was difficult to evaluate. When told the fox and grape fable, she could remember only that it was a story about some grapes. She refused to attempt the test for three minute retention. When asked the capital of Connecticut she said "New Haven, I forget, I knew but I forgot again." In doing simple calculations, depression of memory was apparent, and it would take her some little time to arrive at the correct answer, but she seldom made any actual mistakes. Her general level of intelligence seemed dull, but this factor apparently did not account for her failures in tests of general information and memory. She had no insight into the nature of her illness.

On the basis of the physical examination, mental status, and laboratory findings, a diagnosis of pernicious anemia with symptomatic psychosis was made.

Since she refused to eat voluntarily, the patient was fed by stomach tube. The diet, high in calories, contained 300 grams of raw liver pulp daily, and included orange and tomato juice, cod liver oil, and brewer's yeast. In addition, 3 cc of Lederle's concentrated intra-muscular extract were administered twice weekly during the first month.

Although the characteristic response of reticulocytes to specific treatment was not observed, due probably to a complicating bronchopneumonia during the first week of treatment, a persistent reticulocytosis of 3 to 5 per cent was accompanied by a gradual

increase in the red blood cells, until at the end of five weeks the count was 4,200,000 and the hemoglobin 85 per cent (Sahli)

The mental and physical symptoms also improved steadily, and after 18 days on the gavage regime the patient began to take food voluntarily. The incontinence of urine and feces lasted only another week. At first she was frequently completely disoriented for time and place. She named not only the month but the year incorrectly, and she knew neither what sort of building she was in nor where it was. When questioned insistently concerning orientation, she seemed quite confused. On one occasion when told to eat her liver, since it was good for her, she thought the physician meant that she should eat her own liver, and she appeared frightened. This disorientation and confusion, however, cleared up after several weeks. Her emotional attitude, which in the beginning was childish, demanding, irritable, and uncooperative, improved until she began to take pride in her returning strength and diminished irritability. Massage and exercise were frequently employed. At the onset it was necessary to urge her to undertake voluntary movement, but once she overcame her timidity, she exercised gleefully about the ward. The disturbances in memory likewise improved, although she never clearly recalled details of her first two weeks in the hospital. She was discharged October 14, 1933. At that time orientation was correct, and there was no confusion. She seemed a little stupid and still was afraid of blood tests, etc., and was obviously dependent on her sister's judgment. The knee jerks were normal, but she would not relax sufficiently to permit testing her ankle reflexes. Vibratory sense was absent below the iliac crests. Position sense also was greatly impaired in the feet and slightly diminished in the hands. The red blood count on dismissal was 4,400,000 with 90 per cent hemoglobin (Sahli).

Follow-Up Under treatment with parenteral and oral liver general improvement continued during the next three months. Contact with the patient was lost during the year 1934, and when she was again seen early in 1935 it was reported that she had remained mentally and physically well. This was particularly interesting when it was learned that treatment had been changed to oral liver extract, 25 grams daily, on which the blood count had declined to 3,000,000 red cells and 50 per cent hemoglobin (Sahli). General physical, neurological, and mental examination revealed no changes since discharge from the hospital. Under more intensive liver therapy, supplemented with iron, the blood picture was again restored toward normal.

Case 2 History. M. T., a 50 year old Irish housewife, was sent by her family physician to the Psychiatric Clinic on November 17, 1934 because she had recently been expressing delusional ideas. Little information about the family history was obtainable, but an older sister was said to have died of pernicious anemia in 1923. The patient's husband and two adult daughters were entirely well. Her first child had died shortly after a difficult delivery, her fourth and last pregnancy, in 1916, had ended in a stillbirth.

The patient's personality was described as energetic and introverted. She made few friends, but these friends were very close to her. No mood swings had occurred. Sexual adaptation was normal. Details regarding the personality and general history were difficult to obtain because of the low intelligence of the informants. The family as a whole was ignorant and suspicious.

The patient's health had been excellent until the age of 34, when a diarrhea developed insidiously and continued intermittently for seven years. No details of this illness were recalled other than that there was an associated weakness and loss of weight. Recovery occurred spontaneously, and there had been no subsequent gastrointestinal symptoms. In recent years many abscessed and carious teeth had been extracted, and ultimately complete artificial dentures had been procured. An uneventful menopause occurred at the age of 45. The patient's dietetic habits had always been reasonable and moderate, she did not use alcohol. In the past three

years she had complained frequently of palpitation, but there had never been any cyanosis peripheral edema, persistent cough, or unusual dyspnea

During the early summer, about five months before admission, the patient developed an inordinate appetite for bananas, and she would often eat half a dozen in succession, without neglecting her usual diet. Her weight rose within a few weeks from her customary level of 115 pounds to 136 pounds. In spite of this apparent physical well-being, a personality change characterized by increasing irritability and emotional instability was apparent to her family. She was then taken to the mountains for a change of surroundings with the hope of averting a "nervous breakdown." While on vacation she began to lose weight and strength, and on returning home in September she looked tired and worn, and she weighed only 102 pounds.

About a month before admission she began to give evidence of outspoken mental abnormality. She accused her husband of having stolen one hundred and thirty dollars. When he denied it, she accused her niece of having taken the money and ordered this girl, who was single, to leave the house because the patient thought she was pregnant. Furthermore, she accused her husband of being the father of the niece's illegitimate child, and of having a number of other clandestine affairs as well. She wept and cried a great deal. She insisted that her husband sleep in another room and when he did, she was much upset and told him not to desert her. She slept poorly. She also accused her husband of having attempted to poison her food. Her family physician advised that she be sent to a psychiatric hospital.

Both the patient and her family denied that she had ever suffered soreness of the mouth or tongue, pain on swallowing, or indigestion or abdominal distress of any sort. Except for the diarrheal episode mentioned, the bowel function had always been considered normal. There was no recollection of distal paresthesias or tenderness or pains in the limbs, and no awkwardness of the hands or disturbances of sensation or gait. Nor had anyone detected any change in the patient's complexion.

Physical examination disclosed a scrawny, sallow-complexioned woman of pyknic physique with a sad expression and a tired demeanor. Although there was only moderate graying of the hair, she looked much older than her alleged 50 years. Her loose, dry skin had a lemon-yellow pallor, except for the soles and palms which were red. A profusion of telangiectases were scattered over the entire trunk, but none were found on the visible mucosae. Only moderate pallor was noted of the lips and nail beds. The sclerae were muddy, the irides blue-gray in color, and the lenses were slightly clouded. The teeth were replaced by well-fitting upper and lower dentures. The beefy red and deeply furrowed tongue looked abnormally large and its edges and tip were atrophic, there were no ulcers, and the organ was not tender. The abdomen was normal, and neither liver nor spleen was felt. Muscle power in the extremities was moderately impaired. Complete neurological examination yielded nothing abnormal except serious impairment of vibration and position sense from the iliac crests distally. The vital signs were normal, with a blood pressure of 135 systolic and 95 diastolic.

Laboratory Studies The red blood cell count on admission was 2,670,000 with 10.9 grams of hemoglobin (70 per cent Sahli). The white cells numbered 6,700 per cubic millimeter, of which 62 per cent were polymorphonuclear leukocytes and 30 per cent were lymphocytes. In the stained smear the red cells exhibited unusual variations in size and shape, with a definite predominance of very large, oval cells. The Price-Jones curve showed a mean red cell diameter of 8.74 micra, with a dispersion of cell diameters between 5 and 12 micra. The color index was computed to be 1.4. Platelets seemed diminished in numbers in the smear. The reticulocytes remained below 1 per cent for more than a week before effective specific therapy was instituted. By this time the red cell count had declined to 2,300,000. The color index was now 1.65. Since the Van Allen hematocrit indicated 24.5 c.c. of cells per 100 c.c. blood,

the volume index was computed at 124, and the saturation index 13 (Osgood-Haskins)

The urine gave a positive test for urobilin with Schlesinger's reagent on each of two analyses, but was otherwise normal. The stools were normal on several examinations. Gastric analysis revealed hyposecretion and absence of free hydrochloric acid even after the stimulation of ingested alcohol and injected histamine. Roentgenographic examination of the gastrointestinal tract indicated moderate dilatation and slight stasis in the first part of the duodenum, with a very questionable constriction in the descending loop. The Kahn test of the blood was negative, the icteric index was 7.0 and the non-protein nitrogen was 26 mg per cent. The cerebrospinal fluid was normal in pressure, contained no cells, gave a negative test for globulin, and the Wassermann and colloidal benzoïn reactions were negative.

~~Mental Status~~ On admission the patient was correctly oriented in all three spheres, and consciousness was clear. The next day, however, she stated repeatedly that it was 1932 and that she was in a private home. Speech was normal at the sensorimotor level, and the general motor status was not remarkable. She seemed somewhat sluggish, but no retardation of thinking was present. The stream of speech contained no intrinsic abnormalities. Attention and distractibility were within normal limits. There was an obvious, but loosely integrated paranoid trend. She said her husband was trying to kill her, that he had stolen money, and that he had done many cruel things to her at home. She believed that her food had been poisoned at home, and that "dope" was being put in it at the hospital. She thought the doctors were trying to kill her by draining her excessively of blood in doing blood counts. She was suspicious of every diagnostic test. She had no insight whatever into the fact that she was ill. She said there was no reason for her to be in the hospital, that all she needed was fresh air and that she had no anemia. Her emotional attitude was gloomy and pessimistic. At times brief weeping was observed. Her intelligence was rather dull as estimated from her grasp of general information. She would not cooperate in formal tests of calculation, and it was difficult to test her memory for the same reason. No impairment of recent memory was observed in casual conversation, but she did not recall events in the remote past very accurately.

On the basis of the physical examination, laboratory findings, and mental status, a diagnosis was made of pernicious anemia with symptomatic psychosis.

Course in Hospital During the first two weeks of hospitalization the patient ran an elevation of temperature of one-half degree F. for which no cause was discovered, and the red cell count fell to 2,300,000. Effective therapy was then instituted, and the patient received daily intramuscular injections of 2 c.c. of extract derived from 10 grams of hog liver. A typical, pronounced reticulocyte shower began on the fifth day of treatment, reached its maximum on the seventh day, and was followed within 10 days by an increase in the red blood cells of 900,000 per cubic millimeter and a rise of 12 per cent in hemoglobin (Sahli). Four weeks later the red cell count had reached 4,100,000 and the hemoglobin was 90 per cent. Concomitant with this remission in the blood, the patient's general appearance improved, the glossitis disappeared, she ate better, and her strength increased, although there was no gain in weight.

Disorientation was never observed after the first week in the hospital. On several occasions during the first week of hospitalization brief periods of nocturnal confusion were observed, during which she wandered about looking for the bathroom, although she had used it on many occasions. In spite of the improvement in her physical condition and the disappearance of the mental organic symptoms, no improvement occurred in her delusional trend. She continued to be highly suspicious. She accused the nurses of sticking pins in her, said the physicians were poisoning her, and implied that the liver extract given her was dope. She would hide when physicians came on the ward, and was always apprehensive at night when the physician

and nurse entered her room while making rounds. She repeatedly said that cars passing by the hospital contained enemies. She claimed once that the nurses had phoned for a hearse to take her away. At no time, however, did she develop a systematized delusional trend. She was removed from the hospital against advice on January 5, 1935, seven weeks after admission, to continue under the care of her family physician.

Follow-Up Ten weeks after discharge the patient was visited in her home. At that time her mental status was entirely normal, and apparently she had been sufficiently well to resume her usual household duties and responsibilities. She recalled the details of her hospitalization and said that her attitude had been foolish and unjustified.

It was learned that the patient had neglected all treatment for about six weeks after returning home, but at the insistence of her family she had, in the past month, returned to her physician and was receiving intramuscular injections of liver extract weekly. Shortly after this resumption of treatment her paranoid ideas and apprehensive attitude suddenly vanished. In spite of the lapse in treatment the patient had no complaints, she looked well, there was no glossitis and she appeared to have gained in weight. However, her red blood cells numbered only 3,700,000 and her hemoglobin had fallen to 76 per cent (Sahli). The blood smear revealed slight macrocytosis with hypochromia. Supplementary treatment by the daily oral administration of iron was recommended.

Case 3 History A. K., a 43 year old American housewife, was admitted to the Psychiatric Clinic on January 29, 1935 because she had developed delusional ideas while under treatment for pernicious anemia.

The ancestral stock was German. The family was said to have been characteristically of sturdy body build. The patient's mother had died at the age of 62 of an illness allegedly associated with anemia. There was no history of nervous or mental disease in the family. She had had four children, and they were living and well.

The developmental history was not noteworthy. The patient had first married at 16, and two years later she divorced her husband presumably because he had developed gonorrhea. Her second marriage, at 28 had continued entirely happy. She had renounced the Catholic church in remarrying.

The pre-psychotic personality showed no striking abnormality. Her chief interests lay in her home and family and she was considered a competent housewife, friendly and pleasant. She was subject to short outbursts of violent temper, but no mood swings were known to have occurred. The past medical history contained nothing of significance. She did not use alcohol habitually. Menstruation was still regular.

About 18 months before admission she began to fatigue easily, noted palpitation, and complained of vertigo and dyspnea on slight exertion. Her family physician diagnosed pernicious anemia, and she received specific treatment irregularly from that time on. When her symptoms were alleviated she was prone to discontinue treatment until the complaints returned with the ensuing relapse. At no time did she complain of soreness of the mouth or tongue, indigestion, abdominal pains, diarrhea, or distal paresthesias. Her condition took an abrupt turn for the worse three weeks before admission, at which time she suddenly became irritable and excited, and complained that people were talking about her. She maintained that the landlord and the neighbors upstairs were telling everybody that she had gonorrhea. She said that her husband was conspiring against her and was planning to do away with her. She became very dejected, suffered severe crying spells, and worried over what was to become of her. She often imagined that her sons were fighting among themselves and with the neighbors. During the few days just before hospitalization she would repeatedly call her physician on the telephone to be reassured that she did

not have gonorrhea. Her condition became so disturbing that the physician finally recommended her admission.

Physical Examination There was a slight fever with a temperature of 100° F by rectum. The patient was decidedly obese, weighing 170 pounds although only 62 inches in height. She was of a definitely pyknic body build. The hair was light brown, the eyes blue-gray, and the skin had a characteristic lemon tint. The sclerae were subicteric, and the mucous membranes were pale. There was no papillary atrophy of the tongue, and the organ was not reddened or sore. The heart was normal in size, the heart sounds were normal. There was no ascites, no dilatation of the abdominal veins, and no other signs of portal obstruction, the liver and spleen were not felt. Moderate pitting edema of feet and legs extended almost to the knees. No varicose veins were seen, and no focal tenderness, redness or swellings were noted. There was no lymphadenopathy. A complete neurological examination revealed absent knee and ankle jerks. The plantar reflexes were normal. Vibration sense was found impaired from the iliac crests distally, and was completely absent at the malleoli. There was slight awkwardness of the hands and fingers in attempting fine movements.

Laboratory Examinations The red cell count of 1,950,000 was associated with 8 grams of hemoglobin (50 per cent Sahli). Of the 5500 white cells per cubic millimeter, 69 per cent were polymorphonuclears, and 30 per cent were lymphocytes. Platelets appeared to be reduced in numbers in the blood smear. Marked anisocytosis and poikilocytosis with conspicuous macrocytosis were confirmed by a Price-Jones curve revealing a mean red cell diameter of 8.23 micra with a dispersion of cell diameters between 5 and 12 micra. One normoblast and two megaloblasts were seen. Several urine analyses were negative except for the presence of urobilin. No free hydrochloric acid was found on gastric analysis even after the injection of histamine. The stool examination was negative. Lumbar puncture revealed normal cerebrospinal fluid. The blood Kahn was negative, the icteric index was 12, the total serum proteins were 6.10 grams per cent, and the non-protein nitrogen was 31 milligrams per cent. No organic lesion of the gastrointestinal tract was discovered by roentgenographic examination.

Mental Status On admission, orientation was correct for place but fluctuated for time. A few hours after admission the patient thought she had been in the hospital two or three days, and she could not give the day of the week correctly. There was no other evidence of confusion. She was sluggish and inactive, but the motor status showed no other abnormality. Speech was normal at the sensorimotor level. The stream of speech was somewhat circumstantial. Thought processes were moderately retarded. Repeated fits of weeping were observed. She said, "I don't know why people should say things like that. Maybe I do have a disease. I don't know. Do you think I have?" Her delusional ideas were consistent with her depressed mood. She misinterpreted voices in the corridor and believed that people were talking about her. Memory for recent events was poor. This was not so evident on admission, but during her course in the hospital it was repeatedly demonstrated that she did not recall clearly details of events happening a few hours or days previously. She herself admitted that she could not think as clearly or recall things as readily as formerly. Her intelligence as judged by her general information seemed about normal. She was able to repeat fables and to recognize their significance satisfactorily. Memory for rote material was not good. She gave wrong answers in subtracting successive 7's without detecting the errors. She apparently had some insight into her condition. She knew she had pernicious anemia and that she was nervously ill, but insisted that if people would stop talking about her and let her alone, she would get over the nervousness. She did not believe her nervous state had any connection with mental disease.

On the basis of the physical examination, laboratory findings, and mental status, a diagnosis was made of pernicious anemia with symptomatic psychosis.

Course and Treatment After a week of observation without specific treatment the patient was tried on an experimental parenteral liver extract for 12 days without improvement. Treatment was then changed to the oral administration of a commercial autolyzed liver extract. On this regime the blood picture showed a gradual improvement, and in 18 days the hemoglobin reached 82 per cent (Sahli) and the red cell count 2,910,000. This improvement was achieved in the face of a continued, unexplained fever of 1° F, and in the absence of the customary reticulocyte shower, the reticulocytes varied between 3 and 5 per cent throughout the period of daily observation. The psychotic manifestations showed no improvement. Depressive mood was at all times obvious, and the patient repeatedly expressed delusional ideas in keeping with the mood. At night pucky episodes would occur, during which she would leave her bed and wander into other patients' rooms, telling them that something dreadful was going to happen to her. She never became correctly oriented for time, and defective recent memory could always be demonstrated.

During the last week in February she complained of weak spells of abrupt onset and short duration. On March 1 she collapsed following a momentary attack of weakness and vertigo, and on this occasion she described a feeling of numbness beginning in the feet and extending upwards into the trunk. Her face was pale, the lips cyanotic, and the respirations slightly labored. Although the pulse felt weak it was not rapid, and the blood pressure had not fallen. The episode passed off within a few minutes only to recur many times more during the following week. The patient recalled having had similar "fits" at intervals for two or three years. On March 10, during one of these attacks, she lost consciousness, the pulse and respirations ceased, and death ensued.

Necropsy by Drs H. M. Zimmerman and D. M. Grayzel revealed an adipose subject with an abundance of yellow fat. The mucosa of the stomach was smooth and pink, and microscopically it appeared atrophic. The large, pale liver weighed 2345 grams, the spleen was also large and weighed 312 grams. Bone marrow taken from a vertebra and tibia showed hyperplasia and, in spite of recent liver treatment, the predominating cells were still megaloblasts, myelocytes, and erythroblasts. The red cells appeared distorted, very little fat tissue was present. Striking changes in the central nervous system included destruction of medullary nerve fibers and a reparative gliosis in the posterior columns and lateral pyramidal tracts of the spinal cord, as well as a degeneration of spinal ganglion cells. Definite nerve cell destruction was also apparent in the brain, especially in the frontal lobes.

A large, organizing thrombus was situated in the left femoral vein. The right pulmonary artery was completely occluded by a friable gray-brown clot, and several smaller branches of the left pulmonary artery were similarly plugged. A few small zones of infarcted tissue were found in the left lung.

DISCUSSION

Our three cases resembled one another in that they all showed the fundamental symptoms of an organic psychosis. The first patient seemed confused on admission, and disorientation was observed on several occasions before improvement in the mental picture began. She was very easily fatigued, her attention was poor, and her intelligence was dull, but we did not feel that these features accounted for the disorientation and confusion. Memory seemed impaired at first but gradually improved, as did the other organic mental symptoms, under specific treatment.

In the second case, although the patient was clearly oriented on admission, disorientation for time and place was observed two days later as well as on several other occasions. Brief episodes of nocturnal confusion were observed, which we believed likewise indicated clouding of consciousness. Memory seemed poor but showed no striking change and was difficult to evaluate because of her limited intelligence. The defects in orientation and the episodic confusion improved under treatment.

The third patient was found to be definitely disoriented for time on a number of occasions, and recent memory defects were demonstrated repeatedly at times when her attention and cooperation were satisfactory. No improvement in the symptoms occurred during two weeks of specific treatment, after which her death from a pulmonary complication terminated our observations.

The opinion of the psychiatric staff was unanimously in favor of a diagnosis of symptomatic psychosis in all three cases on the basis of the organic symptoms we have just discussed. It was recognized, however, that the content of the psychosis and the affective symptoms in each case could be understood only in terms of the total personality and its way of experiencing.

The first patient was a middle-aged spinster of low intelligence who always had been childishly dependent upon her family. During her illness her helplessness became exaggerated. She demanded attention from the nurses and constantly called upon her sisters for advice and sympathy. At first she refused to cooperate with treatment and even induced vomiting deliberately. She was timid and was afraid to try to walk after her strength began to return, so that it was necessary to handle her firmly, as one would a refractory child. Eventually, however, she took a childish delight in her recovery. No affective depression ever was seen, and no hallucinations or delusions were elicited. The picture superficially resembled an extreme invalid reaction of the so-called neurasthenic type in a person of low intelligence, but we felt that the additional confusion and disorientation indicated the correct diagnosis of symptomatic psychosis.

The clinical picture in the second case resembled agitated depression. Little reliable information was obtained concerning the patient's pre-psychotic personality, so that it was difficult to interpret the content of the psychosis in terms of previous experience. She manifested the extreme suspiciousness and vague paranoid trend described by Barrett¹ in his cases. The organic mental symptoms improved under specific treatment, but the affective depression and paranoid trend did not improve, which is not surprising since these symptoms really are personality manifestations and not organic cerebral symptoms. The paranoid depression cleared quite suddenly and without any apparent reason after discharge.

The third patient was obviously depressed and expressed paranoid ideas in keeping with her depressed mood. The delusional content of the psychosis was understandable in terms of her past experience. The disorienta-

tion for time and memory defects were definite, however, so that we believed that symptomatic psychosis was the correct diagnosis although the picture in other respects was not distinguishable from manic depressive psychosis

It is interesting to review briefly the relationship between the physical and mental disturbances in these cases. In our first case a symptomatic psychosis was present when the erythrocyte count was 3,200,000 per cubic millimeter. We did not believe that this degree of anemia was in itself sufficient to produce a psychosis. Furthermore, although the mental disturbance improved under treatment while the erythrocyte count was rising, no mental symptoms were present 18 months later when the red cell count had fallen to 3,500,000 per cubic millimeter due to insufficient treatment. In the second case also the organic mental symptoms disappeared while the anemia was responding to treatment, and did not reappear even though the erythrocyte count fell from 4,100,000 to 3,700,000 when treatment was discontinued temporarily. The delusional trend in this case apparently was not affected by treatment, but as we have mentioned above, we consider delusions as personality manifestations and not as organic cerebral symptoms. The third patient died before we were able to study the relation of the symptomatic psychosis to the anemia.

It is apparent that in our cases the character and severity of the mental disturbances bore no consistent relationship either to the degree of anemia or to the extent of the neurologic manifestations. While this on first thought may appear implausible, it seems to us fully as admissible as the analogous, well-established observation that neurologic involvement varies quite independently of the state of the blood, subacute combined sclerosis sometimes appearing long before the actual development of anemia. Goldhamer et al.⁹ on the basis of wide experience also have observed that cerebral manifestations may occur either alone or in association with cord disturbance, that they may be present with or without evidence of anemia, and that they may present themselves as the earliest and only manifestations of pernicious anemia.

SUMMARY OF CASES

1 C C, a spinster of 50, with a family history of mental disease, had been ill one year with insidious development of symptoms of anemia, followed after a few months by gait abnormality and mental disturbances. Exacerbation of symptoms by a severe emotional upset led to physical invalidism and precipitated a frank psychosis with confusion, disorientation and memory defect, no insight. Neurological signs of advanced dorsal column degeneration affecting the legs, atrophic glossitis, and achlorhydria were found. Hyperchromic, macrocytic anemia of moderate degree responded well to liver therapy, as did the mental and neurological symptoms. During the ensuing two years the mental and physical improvement was

well maintained in spite of moderate fluctuations in the anemia due to irregular treatment

2 M T, aged 50, housewife, had a family history of pernicious anemia. A seven year episode of diarrhea occurred in early adult life. She was ill five months with irritability and emotional instability followed by rapid decline of weight and strength, the late appearance of outspoken mental abnormality with paranoid delusions and fluctuating disorientation and confusion, no insight. Emaciation, glossitis, and signs of advanced dorsal column degeneration were associated with a moderately severe hyperchromic, macrocytic anemia as well as urobilinuria and achlorhydria. Liver therapy evoked a typical hematopoietic response, with rapid remission of anemia, improvement in general well-being, and early disappearance of disorientation and confusion. Paranoid ideas persisted two months longer and then vanished in spite of temporarily irregular and inadequate liver therapy.

3 A K, housewife of 43, had been diagnosed pernicious anemia two years previously but had accepted liver therapy irregularly and inadequately, with resultant exacerbations and therapeutic remissions. Three weeks before admission she suffered abrupt onset of irritability and excitement with disorientation, memory impairment, depression, and delusional ideas, little or no insight. The patient was obese with a sub-icteric pallor, and pitting edema of the legs. Neurological signs indicated early dorsal column degeneration. Severe hyperchromic, macrocytic anemia with leukopenia was associated with achlorhydria and slight bilirubinemia. Incomplete therapeutic remission, readily induced under liver therapy, was accompanied by no physical or mental improvement, and was terminated by sudden death with pulmonary embolism. Necropsy revealed degenerative lesions of the brain and spinal cord, atrophy of the gastric mucosa, enlargement of the liver and spleen, and a megaloblastic bone marrow with hyperplasia.

SUMMARY

1 Three cases of pernicious anemia with symptomatic psychosis are described.

2 None of the patients had shown indication of organic mental disturbance before the development of pernicious anemia.

3 In all three cases symptoms indicating an organic disturbance of cerebral function were observed.

4 In all three patients additional symptoms occurred which were related to previous experience and ways of reacting to the environment rather than to organic cerebral disturbance.

5 Two of the patients were obviously depressed and paranoid.

6 The organic mental symptoms responded to specific treatment in two cases. The third patient died of pulmonary embolism before adequate treatment had been given.

7 None of the patients showed evidence of severe subacute combined sclerosis

8 There was no apparent relationship between the degree of anemia, the severity of the psychosis, and the extent of neurologic manifestations

REFERENCES

- 1 BARRITT, A M Mental disorders and cerebral lesions associated with pernicious anemia, *Am Jr Insanity*, 1913, lxi, 1067-1078
- 2 LURIE, L A Pernicious anemia with mental symptoms, *Arch Neurol and Psych*, 1919, ii, 67-109
- 3 WARBURG, E J, and JORGENSEN, S Psychoses and neurastheniae associated with achylia gastrica and megalocytosis, and the relation between this syndrome and pernicious anemia (a) Psychoses, *Acta med Scandinav*, 1928, lxx, 537-592 (b) Neurastheniae Remarks on the diagnostic form of color and volume indices, *Acta med Scandinav*, 1929, lxx, 193-215
- 4 HACKFIELD, A W Studies of the etiological relationship between the somatic and psychotic disturbances in pernicious anemia, a critical review, *Jr Nerv and Ment Dis*, 1932, lxxvi, 31-48
- 5 SMITH, L H Mental and neurologic changes in pernicious anemia, *Arch Neurol and Psych*, 1929, xxi, 551-557
- 6 SMITHBURN, K C, and ZERFAS, L G The neurological symptoms and signs in pernicious anemia, *Arch Neurol and Psych*, 1931, xxv, 1100-1110
- 7 AIRFENS, R S Neurologic aspects of primary anemia, *Arch Neurol and Psych*, 1932, xxviii 92-109
- 8 GRINKER, R R, and KANDEL, E Pernicious anemia, results of treatment of the neurologic complications, *Arch Int Med*, 1934, lx, 851-871
- 9 GOLDHAMER, S M, BRITTELL, F H, ISAACS, R, and STURGIS, C C The occurrence and treatment of neurologic changes in pernicious anemia, *Jr Am Med Assoc*, 1934, cxi, 1663-1667
- 10 KAHN, E Psychoses complicating other diseases, *Yale Jr Biol and Med*, 1935, vii, 215-223

OLEOTHORAX CLINICAL AND EXPERIMENTAL

By J N HAYES, M D, *Saranac Lake, New York*

THERAPEUTIC pneumothorax is being used more and more in the modern treatment of pulmonary tuberculosis. During the course of collapse-treatment various difficulties and complications may occur. The lung may reexpand prematurely, especially when adhesions are present and when the organ is held under partial compression. On the other hand, it may be impossible for the lung to unfold on account of dense fibrosis in it and in the pleura at a time when the disease is considered healed. Loss of elasticity as a result of the development of a large amount of fibrous tissue around a cavity may prevent its closure in spite of elevation of intrapleural gas pressure. A very mobile mediastinum may be bowed over toward the opposite side, so that increased amounts of gas introduced enlarge the pleural space instead of having the desired effect of permitting further collapse of the lung. Tuberculous empyema may develop and persist for many months, leading to expansion of the lung and debilitation of the patient. In certain patients all of these difficulties can be overcome by replacing the gas in the pleural cavity with oil.

Oil is an irritant to the pleura resulting in thickening and fibrosis. Due to its incompressibility and its weight it maintains a better collapse than does air, the latter allowing some expansion with each inspiration. However the presence of oil minimizes the formation of pleural exudate is in doubt, but it may be related to the surface tension of the oil. Although both olive oil and gomenolated paraffin oil have been shown to affect the acid-fastness and ability of growth of tubercle bacilli in vitro,¹ normally staining bacilli have been seen in the pleural effusions developing under oil. The beneficial effect of oleothorax on tuberculous empyema may not be due to direct action on the bacillus but to stimulation of the reactive cells of the body. The slow absorbability of oil has certain advantages. But its irritating quality and the dense shadow it casts over the shadow of the lung in the roentgen-ray film are occasional disadvantages. Its worst feature is the damage it can do to the lung when it leaks into that organ.²

Paraffin, or mineral, oil is used when one desires prolonged collapse without the necessity of many refills. It is also employed by some to prevent the reformation of pus, others prefer vegetable oil for this purpose. Olive, cotton seed, corn, rape seed, and poppy oils have all been used in the pleural cavity. A difference of opinion exists as to whether vegetable oil is less irritating than mineral oil.³ The latter is more stable and does not become hydrolyzed or rancid, a change which must be avoided when using

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935

vegetable oil Virgin olive oil is more neutral than that obtained from later pressings of the olive

The conflicting views as to which is the more irritating to the pleura, mineral oil or olive oil, are based on both clinical and experimental observations Matson⁴ and Kuss,⁵ for instance, find paraffin oil milder than olive oil in its action on the human pleura, and my own experiments on rabbits show no real difference in their irritative qualities These opinions, I believe, differ from those held by most workers Some believe that the effect of oil is due principally to its mechanical action, some that its modus operandi is through irritation of the pleura, and some believe it has an irritant action on the lung Those who believe in its irritative effect seek a marked pleural reaction by giving large doses of oil at the first filling⁶, or, eschewing compressive action, use only negative intrapleural pressures, and recommend not filling the pleural space with oil as its weight is not necessary to close a pulmonary cavity⁷ To complicate the problem still more there is the question as to whether it is better to use vegetable oil—because it is absorbed into the lung more quickly and more completely than is mineral oil Several experimenters have found that the lung reacts quite markedly to absorbed oil⁸ This may be beneficial when one desires a stimulation of fibrosis to close a cavity, but it may exercise a deleterious effect on re-expansion Regarding the effect of oil on pleural pus, Ross and Tulloch would choose olive oil on the grounds that the higher the acid content the greater the lethal effect on tubercle bacilli (acid value of paraffin oil zero, of neutral olive oil 0.07 per cent) It is, therefore, evident that definitive conclusions have not been reached regarding what oil to use and even for special indications, whether oil is as useful as gelatin for empyema⁹ or as salt solution for compression¹⁰

Gomenol, an aromatic oil, is frequently added to oil when it is injected to control tuberculous empyema Its antiseptic action is rather feeble and some operators do not use it at all Injected in full strength into the uninfected pleural cavity of the rabbit it causes an intense reaction and the animal dies within 24 hours¹¹ Several patients have exhibited general reactions which seemed to indicate a toxic effect of gomenol (Matson, Bernou, Serio¹²) Probably not more than a 10 per cent dilution of gomenol in the chosen oil should be employed Good results have been obtained with metaphen, and the Germans generally use iodipin

EXPERIMENTAL OLEOTHORAX

The various oils injected into the pleural cavity of the laboratory animals cause quite similar reactions Tuberculous pleurisy is difficult to obtain experimentally and most of the experiments have been performed on uninfected animals, some on animals with pulmonary disease Early reports on such experiments showed that the injected oil led to the development of extensive pleural adhesions, though, in patients, oleothorax has been successfully employed to combat this very condition Oil injected into the

virgin pleura frequently causes the formation of an exudate. This effect may be valuable in the human case when one wants to thicken and stabilize a movable mediastinum. Congestion of the pleura is an early reaction and small hemorrhages are not at all uncommon. The membrane becomes infiltrated with pus cells and clasmatocytes, the latter phagocytizing the oil and appearing as large "foam" cells and giant cells. Fibrin is deposited into and on the pleura and organization of the infiltrated and fibrinous tissue soon leads to fibrosis. Vegetable oil becomes emulsified and is carried into the lung by way of the dilated lymphatics and in phagocytic cells.¹³ Some of it undergoes lipolytic action here,¹⁴ and some in very finely dispersed droplets is carried away in the circulating blood and can be found in various organs.¹⁵ The absorption of vegetable oils is much more rapid than that of mineral oil. The thickened pleural membranes become adherent. Bettini finds that the reaction of the lung to the presence of absorbed oil causes a fine pulmonary fibrosis, this may be a factor in healing our human cases.

INDICATIONS FOR OLEOTHORAX

The principal actions of oil blockage are mechanical, irritative and antiseptic.

(a) *Antisymphysis* When the collapsed lung reexpands prematurely, that is, before the disease process for which pneumothorax has been given has healed, all the benefit previously gained is threatened. When the lung attaches itself to the diaphragm, creeps out along it and begins to ascend the thoracic wall, even increased intrapleural gas pressures may not prevent further unfolding of the organ. Usually the tuberculous lesions are in the upper third of the lung, before this portion has reexpanded and while there is still a good selective collapse of this diseased part, only the base being attached to the parietal wall, the gas in the pneumothorax pocket may advantageously be replaced with plain paraffin oil. (Figure 1)

(b) *Compressive* Adhesions may act as guy-ropes, pulling on a relaxed lung and preventing collapse of a cavity. If it is impossible to sever the adhesions or to stretch them out by increasing gas pressures, oleothorax or thoracoplasty must be considered. The latter may be impossible on account of the state of the opposite lung or the general condition of the patient. If the cavity is not too peripheral and if oil pressure can be exerted on the lung surrounding it, the pleural pocket is filled with oil and by repeated injections its pressure is gradually increased in an effort to close the cavity.¹⁶ When the cavity-bearing apex is widely and diffusely adherent, little good can be expected. But if the oleothorax is anterior, the lung being squeezed into the posterior gutter, the chances of success are improved. Some think that oil under pressure is too great a hazard because if a large amount should burst into the lung it might cause suffocation or oil pneumonia. Under the circumstances mentioned above, i.e., an ineffective pneumothorax and surgical means contraindicated or impossible, and with



FIG 1 (A) M K April 24, 1931
mothorax on right since November 1930

(B) June 2, 1933 Cavity may be present on the left as tubercle bacilli are occasionally present General condition excellent



A

B

FIG 2 (A) I B March 16, 1932 Artificial pneumothorax March 1930, multiple cavities, phrenic January 1931, pleural effusion summer 1931 Film shows outlined cavity with base expanded Oleothorax begun April 1932 (B) February 6, 1933 Removal of fluid later shows no cavity at the base

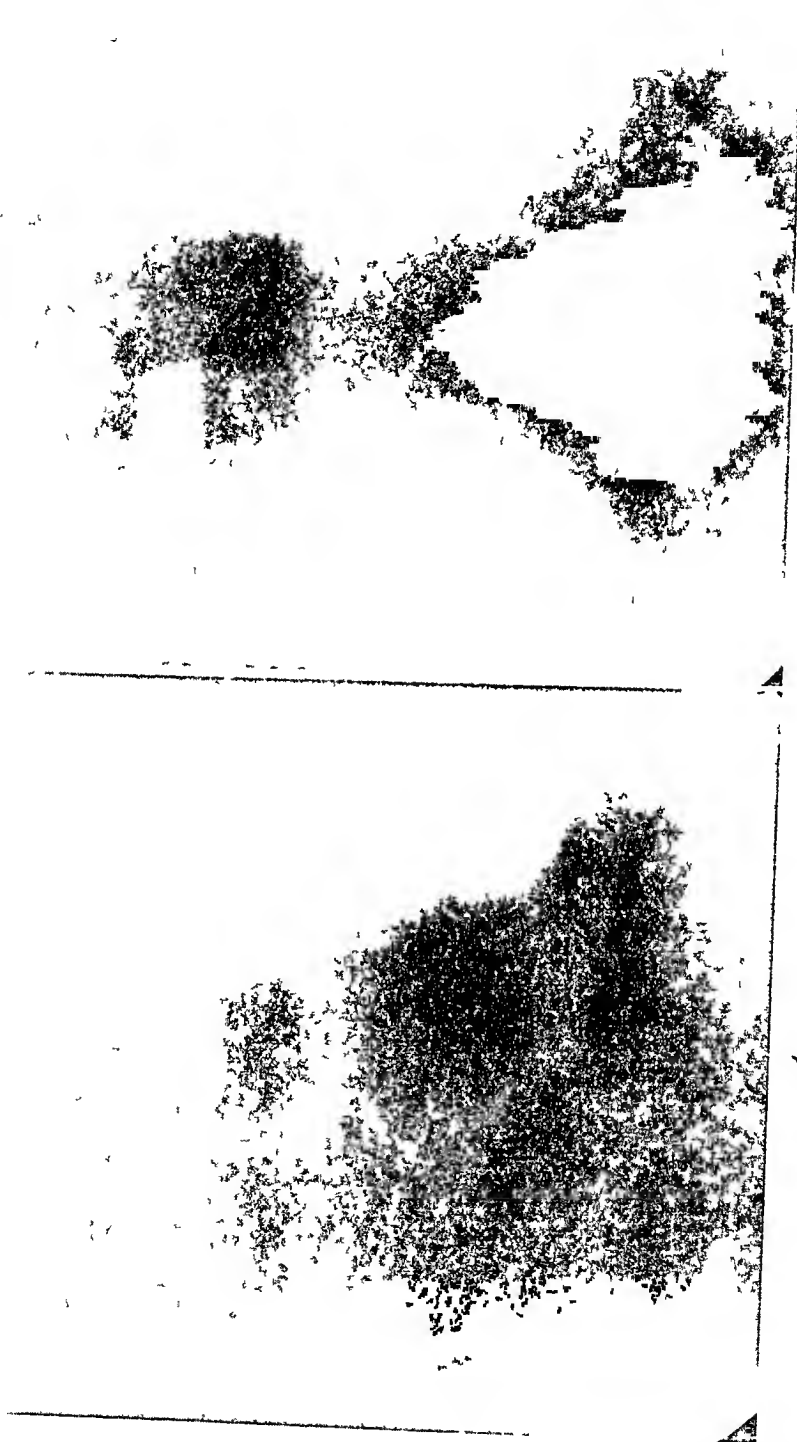


FIG 3 (A) D O Oleothorax for tuberculous empyema
(B) Appearance of lung after aspiration of oil Lung did not expand, it merely retracted to right

the cavity not too peripheral, oleothorax is indicated. Kuss thinks that high oil pressure is less dangerous than the fluctuating pressure of hypertensive pneumothorax (Figure 2)

(c) *Antiseptic* When tuberculous empyema develops and the pus continues to reform in spite of repeated aspirations and irrigations of the pleural sac, the remarkable drying-up action of oleothorax is most satisfactory (Figure 3). Pleural lavage should always be tried first. When the empyema is causing grave symptoms, oil has a definite detoxifying action, an effect not unexpected after Clerc's experiments on the neutralizing action of gomenolized oil on various exotoxins, the blocking of lymphatics and its inhibitory action on acid-fast organisms. Even if the pus reforms, the improvement in the patient's condition may prepare him for collapsing operations which he could never withstand during the early period of grave tuberculous empyema. Dumarest¹⁷ and Bernou warn that oleothorax is contraindicated in malignant tuberculous pyothorax because little benefit can be expected and time is lost before more radical operations. Some patients have been cured, nevertheless.¹⁸ Primary tuberculous empyema, i.e., occurring without previous therapeutic pneumothorax, yields very excellent results with this treatment. Some cases of mixed infection by tubercle bacilli and other organisms have been cured with oleothorax but better antiseptics are available, if oleothorax is employed the use of 20 per cent gomenol in oil is recommended.

(d) Sometimes after sufficiently prolonged pneumothorax, the lung has become so fibrous or is so bound by an unyielding pleura that it will not re-expand. If air refills are stopped, the lung is drawn toward the thoracic wall which becomes greatly retracted and the mediastinal organs are drawn over and perhaps twisted. Circulatory symptoms and pain or discomfort from the increased negative pressure sometimes result. The onset of this distress becomes evident before the lung has reached the chest wall. To correct this the operator may choose permanent pneumothorax, oleothorax or thoracoplasty. In some cases oleothorax is best.

(e) *Bronchopleural Fistula* If the perforation is large, or low in the pleural cavity, oleothorax is contraindicated. In fact, many operators refuse oil treatment to any fistulous patient. The best indication is said to be suffocating pneumothorax with valvular fistula if attacks recur.¹⁹ Bernou²⁰ well expresses the limitations of the use of oleothorax in pulmonary perforation and advises against it when a number of adhesions hold the cavity open, when the perforation connects a cavity with the pleural space or when the pleura is thick and the parenchyma dense. He admits its usefulness when the pleura is supple and free of adhesions and the lung perfectly compressible. These conditions must seldom occur except when pulmonary perforation is due to a needle wound which nearly always heals unaided. Some successes have been reported when the opening through pleura into lung is minute and intermittent. A very good estimation of its size can be made from various signs. The pleural cavity is not filled

with oil as in the conditions mentioned earlier but the oil level is kept below the level of the fistula, as determined by the usual position of the patient

(f) *Mediastinal Relaxation* This may interfere with collapse of a pulmonary cavity and can be corrected by instilling a small amount of oil which usually causes a pleural exudate with resultant thickening and fixation of the yielding membrane. Air pressures are then exerted against the lung rather than against a mobile mediastinum

(g) Other rare and not generally accepted indications have been offered to avoid air refill reactions, to maintain collapse when it is impossible or inconvenient for the patient to go for refills frequently, etc. Oleothorax demands as much supervision as does pneumothorax treatment and the patient should be under observation. Small amounts of oil have been injected along with the first few air refills to decrease the number of serous effusions of pneumothorax.²¹ Unverricht's²² results were decidedly good, those of Heise²³ fair

(h) *Non-Tuberculous Diseases* Oleothorax has been used to supplement therapeutic pneumothorax in bronchiectasis. Some successes have been reported in acute pyogenic empyema, and in chronic empyema when the lung fails to expand and decortication is dangerous because of pre-existing bronchopleural fistula.²⁴

TECHNIC

Without going into many details the institution and conduct of treatment are based upon experience with collapse therapy. It is usual to test the response of the pleura to small doses of oil injected during an ordinary refill of air, gradually increasing the doses until the pleural cavity has been filled. Except in compressive oleothorax the oil pressure is left lower than atmospheric pressure. The need of a refill is determined from the return of symptoms and by puncture rather than from roentgenologic evidence. Refills may be indicated after a month or two up to a year or more. Mineral oil is absorbed much more slowly than is vegetable oil. The latter is chosen, therefore, by some for treating empyema in the belief that the antiseptic dissolved in it acts more effectively. Unless it is desirable to maintain the oleothorax permanently (as when thoracoplasty is contraindicated or refused), the oil is removed when the purpose for which it has been given has been accomplished. Pneumothorax is then resumed because it is easier to control collapse and reexpansion than with oleothorax.

COMPLICATIONS

With the first injections, especially into an uninfected pleura and even when a few c.c. of oil are used, pleurisy with effusion may occur. The reaction may be severe and the effusion may become purulent. Pleurisy may develop when the chest is full of oil, causing a high pressure which may prove dangerous. Perforation of the lung is the accident which is

most feared. Many of the bronchopleural fistulae discovered during oleothorax are not due to the oil but were present previously and are revealed by the patient's tasting gomenol whose aromatic quality permits its odor to seep through a very small opening which may open and close intermittently. Flooding of the lung with oil may cause death from suffocation. When oil escapes into the thoracic wall through careless technic or from ulceration, a painful and persistent paraffinoma results. With good judgment in the choice of patients and careful technic in giving the treatment, however, serious complications are uncommon.

RESULTS

The table below shows some of the results obtained. They are really

OLEOTHORAX
Results

Indication	Tbc Pyothorax	Anti- Symphysis	Compressive	Bronchial Fistula
270 cases (8 authors) ²⁵ Per cent satisfactory	139 74	94 71	37 54	36 39
Matson, ²⁶ 100 cases Per cent satisfactory	50 60	alone or combined 50 50		
		Complications Per cent (Matson)		
Pur effusion	12 recurred	10		
Bronchial fistula	10	6		
Cutaneous fistula	10	4		
Paraffinoma	0	12		

good when one considers that many of these patients would not have been acceptable for radical thoracic operations and that oleothorax is substituted for pneumothorax when the benefit derived from the latter is threatened or in real jeopardy. The best results are those obtained with "cold," or mild, tuberculous empyema which is not responding to the usual treatment, aspiration and lavage of the pleural cavity, and with prematurely reexpanding lungs especially when the latter are selectively collapsed. Pyothorax in this table includes both mild and grave cases. Matson's results are given separately as being the best and largest series in American literature. Matson's figures show that there is frequently more than one indication in any one patient, for the use of oleothorax. Forty per cent of closures of bronchopleural fistulae seems remarkably high. I have not had a single success.

BIBLIOGRAPHY

- 1 CLERC, J À propos de l'oleothorax Étude bacteriologique et experimentale du gomenol, *Rev de la tuberc*, 1930, vi, 39-75
- MOREL, A, and ROCHAUX, A Sur le pouvoir infertilisant de quelques essences vegetales vis-a-vis de divers microbes pathogenes, *Compt rend Soc de biol*, 1927, 1311 Recherches comparatives sur l'action microbicide des vapeurs de quelques essences vegetales, *Ibid*, 1921, lxxv, 861-863
- COURMANT, P, MOREL, A, and BAY, I Sur le pouvoir infertilisant de quelques essences vegetales vis-a-vis du bacille tuberculeux humain in vitro, *Compt rend Soc de biol*, 1927, xvi, 1313 Sur le pouvoir infertilisant de quelques essences vegetales et de leurs constituants, vis-a-vis des cultures homogenes de bacille tuberculeux humain, *Ibid*, 1928, xcvi, 318-320
- KOLMER, J A Bronchial disinfection and immunization, effects in rabbits of intra-bronchial injections of various chemical disinfectants, *Arch Int Med*, 1933, li, 346-366
- TULLOCH, W J, and others Bacteriological characteristics of 100 strains of tubercle bacilli isolated from sputum, *Tubercle*, 1924, vi, 105-123
- TULLOCH, W J Preliminary report of experimental immunization against tuberculosis in guinea pig by use of "oleovaccine," *Tubercle*, 1926, vii, 218-220
- TULLOCH, W J, and ROSS, G R Further observations upon tuberculosis inoculata of guinea pig, *Tubercle*, 1926, vii, 265-276, 321-332
- WAITZ, C Experimentelles zum Oleothorax, *Beitr z Klin d Tuberk*, 1930, lxxiii, 59-72
- 2 HAYES, J N Dangers and complications of oleothorax, *Jr Thorac Surg*, 1932, ii, 34-43
- 3 SALEY, D H, WILLIS, H S, and ELLWART, L Studies in experimental oleothorax, *Trans Nat Tuberc Assoc*, 1934, 141-145
- WAITZ, C See reference 1
- GOLDENBERG, I, and FLANCHIK, S I Superiority of mineral oil over olive oil in oleothorax, *Am Rev Tuberc*, 1932, xxvi, 754-762
- BETTINI, D Ricerche sperimentali sull' oleotorace, *Riv di pat e clin d tuberc*, 1933, vii, 400-419
- BALLON, H Some experiences with oleothorax, *Am Jr Surg*, 1932, xvi, 1-11
- ARCHIBALD, E Note on compression of lung by paraffin oil in pleural cavity, *Am Rev Tuberc*, 1922, vi, 898-899
- 4 MATSON, R W Oleothorax, *Am Rev Tuberc*, 1932, xxv, 419-468
- 5 KUSS, M G Technique des oleothorax, *Rev de la tuberc*, 1926, vii, 100-116
- 6 COURTOIS, R, and BONAMIS, P Pleuresies provoques et injections massives en plevre saine d'huile gomenolee, *Rev de la tuberc*, 1934, ii, 955-980
- GUINARD, U *Rev de la Tuberc*, 1933, 84-87
- 7 MORIN, J, and BOUESSEE, F À propos de l'oleothorax, *Ann de Med*, 1929, xiv, 331-350
- 8 WAITZ, C See reference 1
- BETTINI, D See reference 3
- 9 HUNTER, R A Gelatinothorax, *Tubercle*, 1931, vii, 204-206
- 10 TRIBOULET, and SORS, M Essais de serothorax, *Rev de la tuberc*, 1933, i, 74-87
- 11 Personal experiments
- 12 MATSON, R W See reference 4
- SERIO, F Incidenti da oleotorace, *Rif med*, 1931, lvii, 835-837
- 13 BINET, L, and VERNE, J Sur l'absorption de l'huile par la plevre, *Compt rend Soc d biol*, 1924, xli, 66-68 Les processus histologiques de l'absorption des graisses par la plevre, *Bull d'histol appliq a la physiol*, 1925, ii, 14-190 (Also in *Ann d'anat pathol med-chir*, 1925, ii, 97-104)
- 14 BRATIANO, S, and BRATIANO, C L'absorption des graisses animales par la plevre, *Bull d'histol appliq a la physiol*, 1928, v, 133-145

- 15 BETTINI, D See reference 3
- 16 KUSS, M G Rapport sur l'oleothorax, Rev de la tuberc , 1928, ix, 714-741
- 17 DUMAREST, F Indications for oleothorax, Rev de la tuberc , 1929, x, 420-423
- 18 BERNOU, A Contribution a l'etude des injections huileuses massives dans la plevre, Rev de la tuberc , 1926, vii, 345-395
 FONTAINE, J Resultat de cent oleothorax, Rev de la tuberc , 1928, ix, 769-774 Oleo-
 thorax indications, technique and results, 1929, G Dom, Paris
- 19 WEIL, P E, and ISCH-WALL, P Treatment of suffocating pneumothorax, Bull et mem
 Soc med d hôp d Par , 1923, xlvii, 127-130
 WEIL, P E, DARBOIS, E, and POLLET Spontaneous pneumothorax and oleothorax, Ibid ,
 1923, xlvii, 1382-1385
- 20 BERNOU, A L'Oleothorax, Presse med , 1932, xl, 1139-1141
- 21 THIN, E L'Oleothorax, 1923, A Legrand, Paris
- 22 UNVERRICHT and DOSQUET Methode zur Vermeidung von Pneumothorax-exsudaten,
 Deutsch med Wchnschr , 1933, lix, 451-452
- 23 HLISE, F H, and PAINE, D Pleural fluids during artificial pneumothorax treatment
 in pulmonary tuberculosis, Trans Am Clin and Climat Assoc , 1934, l, 246-257
- 24 BAUMGARTEN, W, and RUSK, H A Oleothorax, its use in chronic non-infectious
 pleural effusion, South Med Jr , 1932, xlv, 239-242
- 25 DAVIES, W J Use of gomenol in tuberculous empyema, Am Rev Tuberc , 1931, xiv,
 263-275
 LABESSE, P, and MARIE, J C De la place que doit tenir l'oleothorax dans la collapso-
 therapie de la tuberculose pulmonaire, Rev de la tuberc , 1930, xi, 648-666
 FONTAINE, J See reference 18
- MUNRO, N M Oleothorax, with observations on 20 cases, Brit Med Jr , 1932, i, 554-
 558
- DANIELLO, L, and ALEXANDROV, M Analyse des resultats obtenus dans 46 cas de
 tuberculose traites par l'oleothorax, Rev de la tuberc , 1931, xii, 1171-1178
- CARMICHAEL, D A Oleothorax treatment of purulent tuberculous effusions, Canad
 Med Assoc Jr , 1932, xlvii, 160-163
- McMAHON, B T Therapeutic pleural effusions by oleothorax, Am Rev Tuberc , 1932,
 xvi, 424-426
- HAYES, J N, and BROWN, L Experiences with oleothorax, Jr Thorac Surg , 1933,
 iii, 1-11
- BELCIUGATEANU, L, and POPPER, M Sur l'oleothorax therapeutique, Bull et mem Soc
 med d hop de Bucarest, 1924, vi, 240-243
- 26 MATSON, R W See reference 4

CASE REPORTS

GONORRHEAL SEPTICEMIA AND ERYTHEMA NODOSUM*

By HENRY J BAKST, M D, JOHN A FOLEY, M D, and MARION E LAMB,
Boston, Massachusetts

SINCE the report of two cases of gonococcal septicemia by Hewes¹ in 1894 the publishing of sporadic cases has increased that number to about 150. Only 37 of this number, however, have had as fortunate an outcome as the two cases described by Hewes. We have recently had the opportunity of observing a case of gonococcal septicemia complicated by the presence of erythema nodosum. The fact that this patient was still entirely well when seen 14 months after his discharge from the hospital is, we believe, a source of added interest.

CASE REPORT

A 42 year old colored porter was admitted to the Boston City Hospital on December 30, 1933, complaining of pain in both legs of about two weeks' duration.

Two weeks before admission to the hospital he noticed the onset of symptoms which were suggestive of an acute upper respiratory infection. On the following day he awoke with aching pains in both legs, and became aware of the presence of large, red, painful areas on both legs. He also complained of fever, chills, nausea, frequency and nocturia.

The family and social histories were essentially irrelevant.

The patient was a widower, his wife having died in 1929. There had been no pregnancies, and the cause of her death was unknown to the patient.

His past history was not remarkable as far as childhood diseases were concerned. He had no knowledge of having had chorea or rheumatism, and had had no known contact with tuberculosis. In 1923 a bullet was removed from his left thigh, and in 1930 he was admitted to the Boston City Hospital for four days because of an acute gastritis following an alcoholic debauch.

Symptoms referable to the cardiorespiratory or gastrointestinal systems were not elicited. He gave a history of gonorrheal infection in 1926, but denied lues by name and symptoms. He weighed 148 lbs. on admission to the hospital, and his best weight had been 154 lbs. six months previously.

Physical examination revealed a well developed and well nourished adult negro, lying quietly and comfortably in bed. The skull, scalp and hair were negative. The ears and eyes were normal. The pupils reacted equally and well to light and distance. A slight painless swelling of the right side of the upper lip was noted in addition to the presence of a small scar on the left side of the forehead. The mouth and throat were not remarkable. The neck was negative save for the presence of slight painless adenopathy.

The thorax was symmetrical and expanded equally and well on both sides. The

* Received for publication July 3, 1935.

From the Fifth Medical Service, Boston City Hospital, the Department of Medicine, Boston University Medical School, and the Mallory Institute of Pathology, Boston.

apex impulse was plainly visible at the fifth interspace in the midclavicular line. The heart sounds were regular and of good quality. No thrills or murmurs were made out. The aortic second sound was slightly more pronounced than the pulmonic second sound. The lung fields were clear and resonant throughout with no râles. The radial pulses were regular, equal, and synchronous with a rate of 76 per minute. The blood pressure was recorded as 128 mm of Hg systolic and 76 mm diastolic.

Examination of the abdomen was negative. No tenderness, masses or spasm were made out. The liver, spleen, kidneys and gall-bladder were not palpable. The genitalia were normal. Rectal examination revealed the presence of a slightly enlarged boggy prostate which was moderately tender on digital palpation. Many pus cells were seen in a smear of the prostatic secretion, but no organisms were noted.

Small, non-tender, firm glands were palpated in both axillae and both posterior cervical chains.

The reflexes and upper extremities were normal. The lower extremities were negative except for the presence of a two-inch scar on the upper and inner aspect of the left thigh, which was the result of an old bullet wound. Two round, red, painful, indurated and symmetrical lesions about two inches in diameter were noted on the anterior surface of both legs midway between the knees and ankles.

The hemoglobin was 80 per cent (Sahli). The leukocyte count, which was 3,600 on admission, rose steadily until January 17, when it reached a peak of 20,500. It then slowly declined, and was 8,500 at the time of discharge from the hospital. The erythrocyte average count was 4,000,000. The differential smear was not remarkable, and no malarial parasites were seen.

Twenty-seven urine specimens showed a variable reaction with a specific gravity ranging from 1.003 to 1.027. Albumin in small amounts was present on four occasions, but sugar was never noted. Microscopic examination of the sediment revealed occasional white cells, rare red cells, and no casts.

The non-protein nitrogen was reported as 42 mg. The Kahn test of his blood was negative. The Widal test was negative. The first blood culture showed a *Staphylococcus albus* contamination. On January 16 the second blood culture was reported as having been positive for *Micrococcus gonorrhoeae*. The next two cultures on January 19 and 20 showed no growth, but on January 24 a second culture positive for *Micrococcus gonorrhoeae* was obtained. On January 29 no growth was again reported, but on January 31 a third culture positive for *Micrococcus gonorrhoeae* was obtained. The eighth blood culture, taken on February 1, was sterile, and on February 6, *Micrococcus gonorrhoeae* was grown from the blood for the fourth time. The next three blood cultures taken on February 11, March 5, and March 8 showed no growth.

All blood cultures were incubated in blood broth. The four positive cultures showed a moderate degree of hemolysis at the end of 48 hours. When grown on a blood agar plate, these organisms were recognized as raised, gray or colorless, glistening, moderate sized, non-hemolytic colonies. On direct smear, the organisms were found to be gram negative, biscuit-shaped diplococci of irregular size and variable staining. Agglutination reactions gave a positive result with antigenococcus serum in a dilution of 1:400, the same organisms agglutinating with antimeningococcus serum in a dilution of 1:200. Sugar fermentations on ascitic agar with the addition of hormone broth showed the invariable ability of this organism to form acid with dextrose and no change with maltose. On the basis of these findings the organism was considered to be *Micrococcus gonorrhoeae*.

On February 9 a skin biopsy taken from one of the nodes on the left leg was cultured in blood broth. This culture, after 144 hours of incubation, showed no growth.

Examination of the spinal fluid revealed no abnormal findings. The stools were negative.

An electrocardiogram taken on January 30 was reported as showing normal sinus rhythm with a rate of 77 per minute. The PR interval was 0.15 second. The QRS interval was 0.08 second. T_1 and T_2 were upright. T_3 was low. Left ventricular predominance was present.

Roentgenoscopic examinations of the abdomen and chest were negative.

The patient received very little treatment other than salicylates by mouth, prostatic massage, and an increased fluid intake. His frequent chills were accompanied by a septic temperature which persisted for eight weeks. His spleen was never palpable nor did he, at any time, develop audible cardiac murmurs.

By February 22, the fever had subsided, and the skin lesions had cleared entirely. He was discharged well on March 14, 1934.

The patient was admitted to the hospital again on April 1935 for the purpose of checking his physical condition. As far as could be determined, he was perfectly well at this time, and the complement fixation reaction, which unfortunately had been omitted during his previous admission, was now negative.

DISCUSSION

With Faure-Beaulieu's² review of 34 cases in 1906, Thayer's³ review of 20 cases at the Johns Hopkins Hospital in 1922, and the more recent surveys by McCants,⁴ Newman,⁵ and Solomon et al.,⁶ it is seen that the question of gonococcal endocarditis has received periodic and thorough attention. McCant noted 100 published cases in the literature up to 1912. Solomon, Hurwitz, Woodall, and Lamb found an additional 48 cases since then. With few exceptions, these cases have all been of fatal issue. Of the total number of cases reported, there are 10 instances in which the patient survived despite the presence of cardiac involvement,^{5, 7-15} a mortality rate of approximately 93 per cent.

It is reassuring to consider that the presence of the gonococcus in the blood stream does not always imply so high a mortality rate. Thomas¹⁶ and Irons⁸ believe that instances of mild gonococcal sepsis, which ordinarily recover, are considerably more common than is usually recognized. Its infrequent demonstration is ascribed to the difficulty in culturing the organism, the relatively small number of organisms in the blood stream in any given case, the ill-defined clinical picture, and the failure to recognize a metastatic lesion as evidence of a possibly demonstrable septicemia.⁸ More recently it has been suggested that an intermittent bacteremia makes the isolation of the gonococcus from the blood stream more difficult.^{17, 18}

A review of the literature reveals 27 reported cases of non-fatal gonococcemia without demonstrable endocarditis.^{1, 17-19, 20-38} These cases, in addition to our own, exhibit certain features which are worthy of note. Without exception they all represent instances of protracted fever. In several cases the presence of an enlarged spleen and of a suggestive rash obscured the true diagnosis for a time because of the obvious possibility of typhoid fever.^{13, 31}

Of the 28 recovered cases, 18 patients (including our own) had skin manifestations. These skin lesions demonstrate with admirable accuracy the skin manifestations of gonorrhea noted by Leon Perrin³⁹ and Buschke.⁴⁰ Eight patients had a maculo-papular rash,^{23, 24, 26, 27, 30, 31, 38} and two of these had additional pustular lesions.²⁴ Three (including our own) had erythema nodosum,^{21, 29} and three patients had a pustular eruption.^{22, 25, 28} Siegal described a pleomorphic papulo-pustular rash with associated hemorrhagic areas.³⁷ In the

remaining three cases one patient had a macular rash,¹⁸ another had a purpuric eruption¹⁷ and the third had an urticarial type of skin lesion³⁴

The simultaneous occurrence of gonococcal septicemia and erythema nodosum in our patient led us to a consideration of the presence of the latter condition. Early observers such as Trousseau,⁴¹ and later, Lendon,⁴² and others,^{43, 44} recognized these skin lesions as a specific infectious disease of unknown etiology. MacKenzie⁴⁵ noted that many of his cases of erythema nodosum exhibited characteristics of the rheumatic state. Others observed that erythema nodosum was often associated with tuberculosis,^{46, 47, 48} and the presence of acid fast bacilli was actually noted in histological sections of the nodes.^{49, 50} These three conflicting points of view in addition to the well supported concept that this disease is due to streptococcal infection^{51, 52} still have staunch adherents.

Ernberg^{53, 54} looks upon erythema nodosum as an early manifestation of tuberculosis and considers it to be an autogenous tuberculin reaction. Wallgren^{55, 56} adheres strongly to the possibility of a tuberculous etiology and has pointed out the occurrence of epidemics of erythema nodosum in tuberculous families. Collis^{57, 58} recognizes erythema nodosum as a type of hyperactive response to different bacterial allergens, and believes that in London, at least, it is most commonly due to tuberculous and hemolytic streptococcus endotoxins. Yet, in a not far-removed clinic, Forman and Whitwell,⁵⁹ although accepting erythema nodosum as a reaction of bacterial allergy, insist that the evidence is in favor of the tubercle bacillus. Symes,^{60, 61, 62} another British observer, recognizes two forms of the disease: an acute specific fever of essentially unknown etiology, and an allergic form of nodular rash which may be associated with rheumatic fever and tuberculosis. In this country, Hess and Berman⁶³ have demonstrated cases of both the tuberculous and rheumatic variety.

The obvious fact that erythema nodosum has been reported in association with at least 13 other conditions has gone almost wholly unrecognized.

As early as 1887, Bradley⁶⁴ noted the occurrence of erythema nodosum as a manifestation of iodism. This was later supported by Perrin⁶⁵ in 1892. Subsequently these skin lesions were noted in association with syphilis,^{66, 67} smallpox,⁶⁸ phlebitis,⁶⁹ meningococcal,^{70, 71, 72} gonococcal^{21, 29} and pneumococcal septicemia,⁷³ leprosy,⁷⁴ septic sore throat,^{75, 76, 77} scarlet fever,⁷⁸ the post-influenzal state,⁷⁹ chronic ulcerative colitis,⁸⁰ lympho-granuloma inguinale,⁸¹ ultra-violet rays,⁸² and rat-bite fever.⁸³

In view of this imposing array of infectious, chemical, and mechanical factors it seems unreasonable to accept, without qualification, any narrow concept of the etiology of erythema nodosum. The evidence in hand seems to agree with the recent views of Goldberg-Curth⁸⁴ who recognizes an idiopathic type of erythema nodosum, the pathogenic organism of which is unknown, and a symptomatic type which may develop in the course of a wide variety of infectious diseases, and as a cutaneous reaction to toxic substances.

In a recent publication Elwell⁸⁵ gives an excellent review of the various theories regarding the etiology of erythema nodosum. He also presents an interesting case of erythema nodosum in which the recurrence of the skin lesions was associated with axillary lymphadenitis and dental sepsis. It is his view that the syndrome of erythema nodosum expresses a reaction to various bacterial allergens, the most important of which is tuberculosis.

SUMMARY AND CONCLUSIONS

1 A case of gonococcal septicemia complicated by erythema nodosum-like lesions with eventual recovery of the patient is presented

2 The literature on gonococcal septicemia is reviewed A study of the recovered cases reveals an estimated mortality rate of 93 per cent in those cases of septicemia suffering from endocardial damage The presence or absence of cardiac damage is an important factor in determining the prognosis

3 Skin manifestations of various types in association with gonococcal septicemia are seen with sufficient frequency to be regarded as an important diagnostic factor Although the most common type is a maculo-papular lesion, any of the skin manifestations of gonorrhea may occur such as urticaria, hyperemia, purpura, and erythema nodosum

4 It is probable that the so-called idiopathic type represents a large group of patients with symptomatic erythema nodosum in whom the causative factors have been overlooked Any patient presenting the symptom complex of erythema nodosum requires careful study and investigation, for the lesions may occur in the course of a wide variety of infectious, chemical, and mechanical processes

BIBLIOGRAPHY

- 1 HEWES, H F Two cases of gonorrheal rheumatism with specific bacterial organisms in the blood, *Boston Med and Surg Jr*, 1894, cxvii, 515-516
- 2 FAURE-BEAULIEU, M La septicemie gonococcique prouvee par la constatation du gonocoque dans le sang circulant, *These de Paris*, 1906
- 3 THAYER, W S On the cardiac complications of gonorrhea, *Bull Johns Hopkins Hosp*, 1922, xxxiii, 361-372
- 4 McCANTS, J M Gonococcus infection of heart, with report of 2 fatal cases due to gram negative diplococcus, *U S Nav Med Bull*, 1930, xxviii, 603-613
- 5 NEWMAN, A B Prognosis in gonococcal endocarditis, review of literature and report of case with spontaneous recovery, *Am Heart Jr*, 1933, viii, 821-833
- 6 SOLOMON, P, HURWITZ, D, WOODALL, M, and LAMB, M E Diagnosis of gonococcus endocarditis, *Arch Int Med*, 1933, lxi, 1-15
- 7 AUBERTIN and GAMBILLARD Endocardite blennorrhagique guerie par la serotherapie antigonococcique, *Bull et mem Soc med d hop de Par*, 1924, xlviii, 512-517
- 8 IRONS, E E Gonococcemia with a report of six cases in which the gonococcus was isolated from the blood during life, *Arch Int Med*, 1909, v, 601-627
- 9 PERRY, M W Gonorrheal endocarditis with recovery, case report, *Am Jr Med Sci*, 1930, clxxix, 599-605
- 10 SCHAEFFER, H, and BARON, P Gonococcemie a localisations multiples, articulaires, cardiaques meningeae et cutanee, suivie de guerison, *Paris med*, 1927, ii, 93-96
- 11 SILVESTRINI, R Poliartrite, endocardite, setticemia gonococcica, *Riv crit di clin med*, 1903, iv, 385
- 12 WITHINGTON, C F A case of malignant endocarditis with recovery, *Boston Med and Surg Jr*, 1904, cli, 99
- 13 DIEULAFOY, G Gonococcic septicemia, *Internat Clin*, 1909, iii, 59-70
- 14 MARFAN, A B, and DEBRE, R Gonohemie a manifestations viscerales multiples chez une fillette de 10 1/2 ans (essais de traitement par le vaccin de Wright et le serum antimeningococcique), *Bull et mem Soc med d hop de Par*, 1910, xxi, 712-723
- 15 BUQUET, S, and JAUREGUY, J M Gonococcemia a localizaciones multiples, *An de Fac de med*, 1927, xii, 755-757
- 16 THOMAS, J D Gonorrheal septicemia, with marked cardiac involvement, *Med Rec*, 1908, lxxiv, 668-670

- 17 WHEELER, G W, and CORNELL, N W Gonococcal bacteremia in woman, with apparent cure by surgical intervention, *Jr Am Med Assoc*, 1930, xciv, 1568-1570
- 18 GARLOCK, J H Gonococcal bacteremia in woman, with cure by surgical intervention, *Jr Am Med Assoc*, 1931, xcvi, 999-1000
- 19 KRAUSE, P Zwei Fälle von Gonokokkensepsis mit Nachweis der Gonokokken im Blute bei Lebzeiten der Patienten, *Berl klin Wchnschr*, 1904, xli, 492-494
- 20 AHMAN, G Zur Frage von der gonorrhoeischen Allgemeininfektion, *Arch f Dermat u Syph*, 1897, xxxiv, 323-334
- 21 ALEXANDRESCO-DERSÇA, C, and JONESCO, D Thyroidite suppuree gonococcique a la suite d'une gonocoecemie avec rhumatisme polyarticulaire et erytheme noueux gonococcique, *Paris med*, 1932, i, 188-189
- 22 Cabot case 13501 An obscure general infection, *Boston Med and Surg Jr*, 1927, ccvii, 1140-1142
- 23 CHEVREL, F Septicemie gonococcique a caracteres de fièvre intermittente, traitement par la vacinotherapie, *Progres med*, 1912, cxviii, 281-283
- 24 FRIEDBERG, C K Gonocoecemia with recovery, report of 4 cases, *Am Jr Med Sci*, 1934, clxxviii, 271-278
- 25 FILLER, W Gonocoecemia with recovery, *Jr Am Med Assoc*, 1933, c, 1149-1150
- 26 JENKINS, J A Gonococcal septicemia, *Brit Med Jr*, 1922, i, 641
- 27 NANUMUSCEL, I, JONNESCO, D, CLAUDIAN, I, and BRULL, A Septicemie gonococcique pure, *Presse med*, 1933, \li, 194-195
- 28 O'BRIEN, T J, and BANCKER, E A, JR Gonococcus septicemia, recovery without cardiac complication, report of case, *New England Jr Med*, 1928, cxviii, 184-187
- 29 PROCHASKA, A Bakteriologische Untersuchungen bei gonorrhoeischen Allgemeininfektionen, *Deutsch Arch f klin Med*, 1905, lxxiii, 184-196
- 30 RUBENSTONE, A I, and ISRAEL, S L Gonocoecemia with recovery, *Jr Am Med Assoc*, 1932, \ci, 1684-1685
- 31 THAYER, W S On gonorrheal septicemia and endocarditis, *Am Jr Med Sci*, 1905, cxxx, 751-779
- 32 WARE, M W Gonorrheal myositis, *Am Jr Med Sci*, 1901, cxlii, 40-45
- 33 WYNN, W H General gonocoeal infection, *Lancet*, 1905, i, 352-355
- 34 SERRANTES-LASERRE, A E Sobre un caso de septicemia gonococica en un enfermo con abceso de prostata, no operado, *Rev de espec*, 1930, v, 259-262
- 35 ZADOC-KAHN, OGLIASTRI, and WAUTHIER Un cas de gonocoecemie grave suivie de guerison, *Gaz de Hop*, 1926, xcix, 1613-1614
- 36 RAVAUT, P, and DUCOURTIOUX Traitement du rhumatisme et des septicemies blennorragiques par les injections intraveineuses de serum antigonococcique, *Ann de dermat et Syph*, 1927, viii, 266-292
- 37 SIEGAL, L A Case of gonocoecus septicemia, *Bull Buffalo Gen Hosp*, 1925, iii, 66-69
- 38 BLOCH, M, and HEBERT, P Fièvre pseudo-palustre gonocoecémique, guerison par auto-vaccinotherapie, *Bull et mem Soc med d hop de Paris*, 1920, xlv, 277-279
- 39 PERRIN, L Des determinations cutanees de la blennorrhagie, *Ann de Dermat et Syph*, 1890, i, 773-792
- 40 BUSCHKE, A Über Erythema bei Gonorrhoe, *Arch f Dermat u Syph*, 1899, \lviii, 181
- 41 TROUSSFAU, A Lectures on clinical medicine, *New Sydenham Society Trans*, 3rd ed, 1868, Lecture VIII, p 239
- 42 LENDON, A A Nodal fever (febris nodosa), synonyms erythema nodosum, erythema multiforme, 1905, *Balliere, Tindall and Cox*, London
- 43 GOSSE, A H Erythema nodosum, an analysis of 100 cases, *Practitioner*, 1913, \ci, 240-252
- 44 COVIBI, J Erytheme noueux chez les enfants, *Arch de med d enf*, 1923, \xvi, 329-342
- 45 MacKENZIE, S Erythema nodosum, especially dealing with its connection with rheumatism, *Brit Med Jr*, 1886, i, 741

- 46 UFFELMANN, J Über die ominöse Form des Erythema nodosum, Deutsch Arch f klin Med, 1876, \viii, 313-318
- 47 MEARA, F S, and GOODRIDGE, M The relationship between erythema nodosum and tuberculosis, with the report of a case, Am Jr Med Sci, 1912, cxliii, 393-397
- 48 BRONSON, E Erythema nodosum associated with tuberculosis, Brit Jr Child Dis, 1918, \v, 91-101
- 49 LANDOUZY, L Erytheme nouveau et septicemies a bacilles de Koch, Presse med, 1913, \xxi, 941
- 50 ARFNA, A Existencia del Mycobacterium tuberculosis en el nódulo del eritema nodoso, Rev Soc argent de biol, 1933, \x, 542-547
- 51 ROSENOW, E C The etiology and experimental production of erythema nodosum, Jr Infect Dis, 1915, \xvi, 367-384
- 52 SLOT, G Erythema nodosum treated with antistreptococcal serum, Lancet, 1934, \i, 600
- 53 ERNBERG, H Erythema nodosum, Nord med tidskr, 1932, \iv, 230-236 (Abstr, Jr Am Med Assoc, 1932, \xcix, 274)
- 54 ERNBERG, H Erythema nodosum and tuberculosis, Am Jr Dis Child, 1933, \lvi, 1297-1307
- 55 WALLGREN, A Epidemisches Auftreten von Erythema nodosum, Beitr z Klin d Tuberk, 1922, \lii, 143-151
- 56 WALLGREN, A Tubercle bacilli in children with erythema nodosum, demonstration by gastric lavage, Am Jr Dis Child, 1931, \xli, 816-822
- 57 COLLIS, W R F New conception of etiology of erythema nodosum, Quart Jr Med, 1932, \i, 141-156
- 58 COLLIS, W R F Erythema nodosum, Brit Med Jr, 1933, \ii, 1162-1165
- 59 FORMAN, L, and WHITWELL, G P B Preliminary observations on erythema nodosum, Guy's Hosp Rep, 1934, \lxxiv, 213-229
- 60 SYMES, J O Erythema nodosum and rheumatism, Lancet, 1907, \i, 207-208
- 61 SYMES, J O The association of erythema nodosum and tuberculosis, Brit Med Jr, 1914, \i, 909
- 62 SYMES, J O Significance of erythema nodosum, Brit Jr Dermat, 1932, \liv, 181-187
- 63 HESS, J H, and BERMAN, S L Erythema nodosum in childhood, Med Clin N Am, 1928, \xii, 49-66
- 64 BRADLEY, E N L'iodisme, These de Paris, 1887
- 65 PERRIN, L Un cas d'erytheme nouveau du a l'iodure de potassium, Marseille med, 1892, \xix, 567-574
- 66 JANSON, A Uber Erythema nodosum bei Lues secundaria, Dermat Ztschr, 1911, \xviii, 1053-1064
- 67 MAZZANTI, C Sindrome di eritema nodoso in una donna con manifestazioni di sifilide recente in atto, Dermosifilografo, 1933, \viii, 505-516
- 68 TULLIS, W L Case of erythema nodosum following smallpox, Lancet, 1927, \i, 654
- 69 ACHARD, C, and ROUILLARD, J Erytheme nouveau complique de phlebite des veines superficielles des membres, Bull et mem Soc med d hôp de Paris, 1922, \lvi, 1113-1115
- 70 MORGAN, H J Chronic meningococcus septicemia, a report of two cases, Bull Johns Hopkins Hosp, 1921, \xxii, 245-254
- 71 MONTGOMERY, L C Chronic meningococcal septicemia, Can Med Assoc Jr, 1929, \x, 266-272
- 72 MASTER, A M Meningococcemia with endocarditis, Jr Am Med Assoc, 1931, \xcvi, 164-166
- 73 SACQUELPEE, E Erytheme nouveau au cours d'une septicemie a pneumocoques, Bull et mem Soc med d hop de Paris, 1921, \lv, 1539-1542
- 74 RIBEIRO DE SOUZA, S Sindrome de eritema nodoso num doente portador de mal de Hansen, São Paulo med, 1932, \i, 5-8

- 75 STONE, W R Erythema nodosum associated with streptococcic faucitis, New York Med Jr, 1923, cxviii, 673-674
- 76 SHEPHEARD, E Septic sore throat complicated by erythema nodosum, Brit Med Jr, 1926, i, 902
- 77 GOLDSTEIN, H I Erythema multiforme and erythema nodosum with streptococcic sore throat, Med Jr and Rec, 1931, cxxxiv, 266-267
- 78 MORITZ, D Two cases of erythema nodosum with scarlet fever, Orvosi hetil, 1934, lxxviii, 645-646
- 79 BOGANOVITCH, V Five cases of post-influenzal erythema nodosum, Arch Dis Childhood, 1930, v, 56-59
- 80 BROOKE, P A Erythema nodosum-like lesions in chronic ulcerative colitis, report of case, New England Jr Med, 1933, cciv, 233-235
- 81 KREEBERG, L Lymphogranuloma inguinale mit Erythema nodosum und aphthosen Erscheinungen am Genitale, Dermat Wchnschr, 1930, xci, 1376-1379
- 82 MILIAN, G Erytheme nouveau par rayons ultra-violets, Rev franç de dermat et de venerol, 1933, ix, 286
- 83 RIPLEY, H S, and VAN SANT, H M Rat-bite fever acquired from dog, Jr Am Med Assoc, 1934, cli, 1917-1921
- 84 GOLDBERG-CURTH, A Pathogenesis of erythema nodosum, Monatschr f Kinderh, 1935, lvi, 249 (*Abstr*, Jr Am Med Assoc, 1935, civ, 1678)
- 85 ELWELL, L B Erythema nodosum and focal infection, Brit Med Jr, 1935, i, 974-975

ENTERIC CYSTS *

By O B MAYER, M D, F A C P, *Columbia, South Carolina*

ENTERIC cysts, sometimes called enterogenous or developmental cysts, are structurally similar to the intestines. Their cavity, containing a mucoid substance, is usually lined by epithelial cells with an underlying layer of lymphoid tissue and smooth muscle. Increasing internal pressure and consequent impairment of blood supply may cause localized atrophy or other structural changes. According to Ewing,¹ their origin is from some bud or pouch along the intestinal tract, and Evans² believes them to be related to the more common diverticula of childhood. The usual location in the ileocecal area may be explained by the fact that there is a remnant here of the vitelline duct or yolk sac. When the proximal end of this pouch remains patent, the result is the typical Meckel's diverticulum.

Since the first description of Fraenkel³ in 1882, Drennen,⁴ Haggard,⁵ and Bradley and Hoke⁶ have brought the total number of reported ileocecal cysts to twenty-eight. Occurrences elsewhere along the intestinal tract have been reported. Slesinger⁷ found an ileal cyst eight feet from the ileocecal valve, Aitken⁸ another ileal cyst, McLanahan and Stone⁹ two cysts in the rectal area, and Jackson and Ewell¹⁰ one in the mesentery of the transverse colon. These structures have been found even in the thorax (Salvin,¹¹ Poncher and Milles¹²) where they probably arise from mediastinal alimentary tract rests. Hughes-Jones¹³ reviews 55 cases.

The majority of cases have been in childhood, although cysts have been reported in both extremes of life. There is no predilection for either sex and

* Received for publication February 28, 1935

there is usually no other developmental defect. Many of the reported ileocecal cysts have been small, the larger ones are rarely more than 10 cm in diameter.

In the local hospital records of over 80,000 patients no enteric cysts have been recorded. In spite of the rarity their clinical importance must be recognized. They may produce confusing symptoms which simulate intussusception, abdominal tumors, cysts of other kinds, appendiceal abscess, and intestinal obstruction. Infantile pyloric stenosis by its projectile vomiting can usually be differentiated from other forms of obstruction. The clinical picture in adults may be vague and misleading. In general, the symptoms are those due to mechanical pressure, such as pain and obstipation. Other symptoms, however, may arise from intracystic infection, or from hemorrhage, or from the weight of a larger mass. In spite of clinical experience, laboratory studies and roentgenography, after the discovery of an abdominal tumor the final diagnosis is frequently deferred until operative exposure, or even until microscopic studies have been made.

CASE REPORT

A 12 year old white boy was first seen in April 1934, complaining of abdominal soreness and swelling of two days' duration. Eighteen months earlier and again two weeks earlier he had fallen, causing abdominal pain for a few hours. Both falls were considered inconsequential. On examination his doctor had found a large protuberance from a tumor in the left upper abdomen. Otherwise, the history was that of a sound, hardy boy.

Examination showed a normal, healthy, afebrile, athletic appearing child, who had walked into the hospital. Nothing of significance was found except a tumor mass in the left hypochondriac and epigastric regions, which extended to the umbilicus. This was smooth and round, tense, slightly tender and immovable.

The blood cell counts were normal. The urine contained a trace of albumin, and a scant number of hyaline casts.

Roentgen-ray report by Dr T. A. Pitts: "Fluoroscopic examination of the chest is negative. The filled stomach is pressed upward by a palpable mass. The stomach and duodenal cap are negative. The remainder of the duodenum which partially encircles the mass is extremely narrow and assumes an unusual course. The jejunum runs anteriorly and is flattened. The practically empty colon is not outlined. The mass is fixed and the distorted outline of the duodenum makes it typical of a pancreatic tumor, probably a cyst." (Figure 6)

Glucose tolerance test, with 70 grams of glucose

Time	Blood Sugar	Urine Sugar
Fasting	100 mg	0
30 min	154 mg	+++
60 min	156 mg	++
120 min	114 mg	0

The pre-operative clinical diagnosis of probable pancreatic cyst was based on the history of abdominal injury, the location and the apparently rapid development of the tumor, roentgen-ray studies and glucose tolerance test findings.

At the operation, performed by Dr G. H. Bunch, there was found attached to the upper surface of the transverse mesocolon and situated well under the cardiac end of the stomach, an irregular, large, cystic mass (figure 1), not adherent, pushing the stomach upward and the transverse colon downward into the pelvis. Its size

and position mechanically widened the duodenal curve, but caused no apparent obstruction. The attachment of the mass to the transverse mesocolon was separated and the tumor removed intact (figure 2), without disturbing the relationship of the viscera and without resection of the gut.

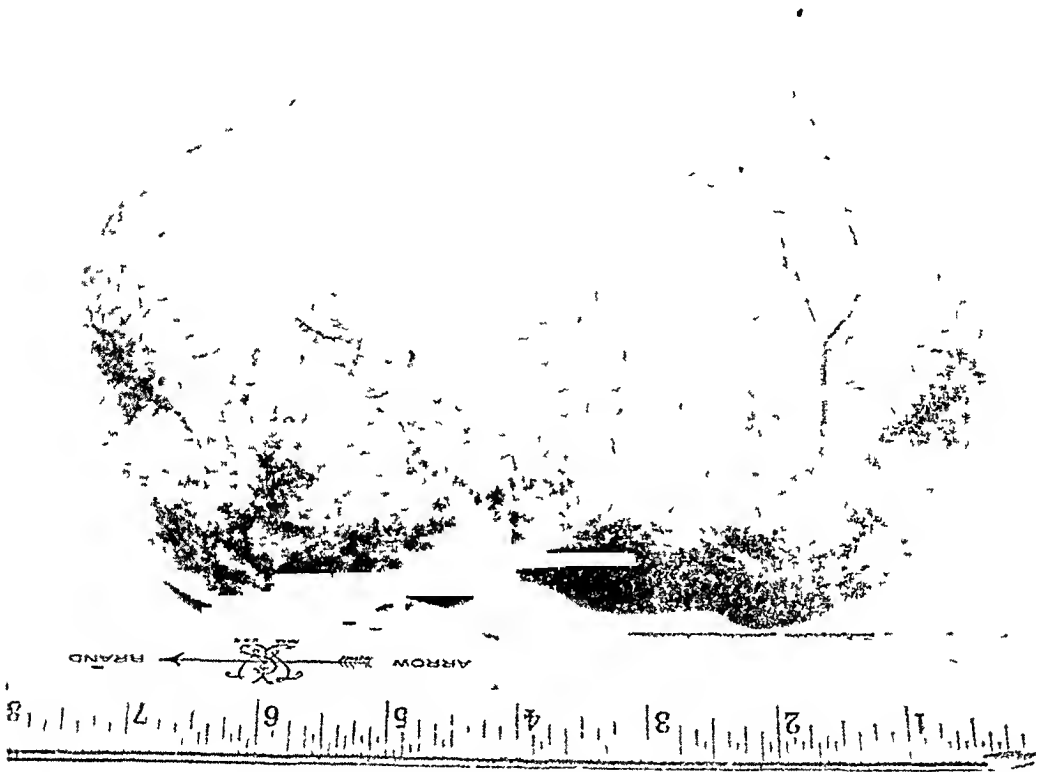


FIG 1 Anterior view of intact cyst (Inch scale)

The pathological report by Dr H H Plowden is as follows. Gross description "The specimen was a cystic tumor weighing 1,563 grams and measuring 20 by 14 by 11 cm. Its outer surface was smooth, glistening, and studded with occasional dense nodules, about 0.5 cm in diameter. The tumor was quite tense, giving the impression of considerable pressure within.

"When the cyst was opened a great quantity of thick, stringy, tenacious mucus of a pale, bluish color with occasional white streaks was seen. The inner walls conformed in shape to the general outside shape, except that toward the point of mesenteric attachment a number of low ridges terminated in sharp edges as if they had at one time divided the large cyst into a number of smaller ones. This finding suggested an originally loculated cyst" (Figure 3).

Microscopic description "Sections made from various parts of the cyst wall show varying structures, apparently depending on the amount of stretching to which the wall has been subjected. The outer surface covering is of flat, pavement-like endothelial cells, which correspond to the peritoneal covering. Beneath this is a layer of thin, loose connective tissue in which are a few small lymphocytes and small

blood vessels The greatest variation of structure is seen in the type of lining cells and in the amount of smooth muscle present In some areas the lining epithelium is a single layer of low cuboidal cells, in others there are several layers of columnar cells, in still others there is a layer of tall columnar cells of the mucus-forming type (figure 4) The latter type of cells predominates In the thinner parts there are



FIG 2 Showing mesenteric attachment (Inch scale)

merely fragments of muscle tissue In some of the thicker areas there is a well developed muscle layer made up of inner circular fibers and outer longitudinal fibers (figure 5) The histological resemblance to intestine is quite striking Diagnosis Enteric cyst"

Convalescence was uneventful and during the 10 months since the operation the boy has been entirely well .



FIG 3 Interior of cyst Atrophic ridges suggest a loculated-type tumor

SUMMARY

Enteric cysts are rare developmental abnormalities which occur anywhere along the alimentary tract although usually in the region of the terminal ileum. Symptoms are usually manifested in early childhood.

This example was found in a 12 year old boy after symptoms of a few days' duration, and the correct diagnosis was made only after microscopic study. The unusual features were (1) its unusual location in the transverse mesocolon, (2) its large size, about one-twenty-fifth of the body weight, and (3) its at-



FIG 4 Section of cyst wall showing single layer of tall columnar cells, many of a goblet type (High power)



FIG 5 Section of entire cyst wall showing similarity to intestinal structure (Low power)



FIG 6 Retouched film showing site of cyst

tachment which permitted intact removal without disturbing the adjacent intestine

BIBLIOGRAPHY

- 1 EWING, J Neoplastic diseases, 1931, W B Saunders, Philadelphia, p 1030
- 2 EVANS, A Developmental enterogenous cysts and diverticula, Brit Jr Surg, 1929, xvii, 34-83
- 3 FRAFNKEL, E Uber Cysten in Darmkanal, Arch f path Anat, 1882, lxxvii, 275-285
- 4 DRENNEN, E Ileocecal cysts, Arch Surg, 1931, xxi, 106-120
- 5 HAGGARD, W D Enterogenous cyst of ileum causing obstruction in infants, Surg Clin N Am, 1930, x, 713-717
- 6 BRADLEY, C E, and HOKE, C C Ileocecal (enterogenous) cyst, Jr Pediat, 1933, ii, 614-615
- 7 SLFSINGER, E G Enteric cyst of large size in boy, Brit Jr Surg, 1928, vi, 333-334
- 8 AITKEN, R Y Cyst of ileum, Brit Jr Surg, 1931, xviii, 521-523
- 9 McLANAHAN, S, and STONE, H B Enterogenous cysts, Surg, Gynec and Obst, 1934, lvi, 1027-1029
- 10 JACKSON, J A, and EWELL, G H Enteric cysts, Wisconsin Med Jr, 1929, xxviii, 118-119
- 11 SALVIN, A A Retroperitoneal cyst, Med Jr and Rec, 1928, cxxvii, 256-259
- 12 PONCHER, H G, and MILLES, G Cysts and diverticula of intestinal origin, Am Jr Dis Child, 1933, xlv, 1064-1078
- 13 HUGHES-JONES, W E A Enterogenous cysts, Brit Jr Surg, 1934, xxi, 134-141

EDITORIAL

THE MOVEMENT AND DISTRIBUTION OF BODY WATER

It is now fairly well established that sodium and potassium, the two principal basic ions present in the body fluids, have a preponderant influence upon the volume and distribution of body water, as well as upon the regulation of osmotic pressure. Approximately nine-tenths of the total osmotic pressure of the body fluids, under normal conditions, is contributed by the dissolved electrolytes. Proteins, urea and other organic substances usually play a distinctly subordinate role. As the contribution of the anions to the total osmotic pressure is about equal to that furnished by the bases, and varies with them, fluctuations in the concentration and excretion of sodium and potassium are of particular significance.

About 70 per cent of the mass of the body is composed of water, which may be separated into two principal divisions from a chemical point of view—the fluid within the cells, and that which bathes the interstitial spaces and comprises the various extracellular fluids, including the blood plasma, lymph and other bodily humors. Owing to the fact that potassium exists in the fluids of the interior of most cells almost to the exclusion of sodium, and that sodium, calculated on the basis of its chemical combining power, or equivalence, accounts for nearly 90 per cent of the bases of the fluids outside of the cells, it is often possible to identify the origin of water discharged from the body by means of the concentrations of these basic electrolytes which are dissolved in it. There is good evidence at the present time, although most of it is indirect, that under ordinary circumstances potassium does not diffuse freely out of the cells and that sodium and chloride do not diffuse into them. The exact amounts of sodium and chloride which are actually present in the intracellular fluids are unknown, but there is reason to believe that at least in many types of cells very little of these electrolytes occur, if indeed they are actually present at all.

In contrast to the relative immobility of the electrolytes, the body water is believed to pass freely in and out of the cell membranes, as required, so as to maintain an equilibrium of the osmotic pressure throughout the body fluids. The pattern of the dissolved substances is fairly constant, but their proper concentrations are stabilized by this shift of water. For the same reason, an excretion of one or both of these ions must necessarily be followed by the excretion of water in order that the concentrations in the body fluids may be maintained at precise level. By studies of the base content of the excreta in disease states, or following the use of diuretic agents, the origin can therefore be surmised. In this manner it has been learned that the dehydration of diabetic acidosis, of severe infantile diarrhea, and following the use of diuretics are all due to a loss of both extracellular and intracellular water. On the other hand, the type present in the condition of heat

cramps, as well as that following the use of thyroxin in myxedema, appears to be due chiefly to a loss of extracellular water

Fluid, however, does not necessarily follow the movement of electrolytes, or at least it may not move in the same direction. Mackay and Butler have recently reported a disproportionate retention of sodium relative to water during the onset of an acute upper respiratory tract infection, and similar retention of sodium, analogous to the well known retention of chloride, has been reported in pneumonia by Sunderman. Darrow and Yannet, by means of ingenious experiments with intraperitoneal glucose, have removed a large portion of the electrolytes of the extracellular fluids without any gain or loss of water from the body, and have demonstrated the profound dehydration and hemoconcentration which results, due to the passage of water into the cells to equalize the osmotic relationships.

A recently studied type of dehydration and resultant hemoconcentration and shock, that following the withdrawal of the adrenal cortical hormone from adrenalectomized animals, is analogous to the type last mentioned. Here a loss of sodium and chloride in the urine is accompanied by a retention of potassium, and the loss of water by way of the kidney may be almost negligible. In this case, in order to maintain the necessary equality of osmotic pressure both inside and outside of the cellular membranes, water penetrates from the interstitial fluids into the cells, lowering the electrolyte concentration within, while at the same time raising that of the interstitial fluids. The consequence, however, is a hemoconcentration, and the symptoms of dehydration and shock which result are practically identical with those seen when actual losses of fluids occur from the body. The observation is of practical interest, since it illustrates anew, the fact that the clinical phenomena which are observed as a result of hemoconcentration, dehydration, and shock, follow chiefly the loss of extracellular fluids. The intracellular fluid, as in this case, may actually be augmented in amount, but this has no effect upon the dehydration. The body does not lose a significant amount of water, but its displacement into the cells renders it ineffective. The fact that the volume of extracellular fluids, as estimated on theoretical grounds, and as measured by means of the sulphocyanate method introduced by Crandell, or by the sucrose and sulphate distribution studies of Leviates, is not large, as compared to the volume of intracellular fluids, may make more significant the loss of smaller amounts of the former than have hitherto been appreciated. These measurements would indicate that the volume of the interstitial fluids is about 20 to 25 per cent of the body weight, while the fluid within the cells themselves may be twice or even three times as much.

G A H

BOOK REVIEWS

Poliomyelitis, a Handbook for Physicians and Medical Students By JOHN F LONDON, M D, and LAWRENCE W SMITH M + 275 pages, 14 5 × 22 5 cm Macmillan Company, New York 1934 Price, \$3 00

This monograph is a very timely addition to the subject of poliomyelitis It is short and concise and yet is inclusive enough to answer any pertinent question concerning the disease The opening chapter gives a short historical review of the subject, with especial reference to Heine and Medin, whose names the disease carries Our present knowledge concerning etiology and pathogenesis is briefly outlined in the second chapter

The pathology of the disease is especially well covered This presentation is based on 96 autopsied cases in the Willard Parker Hospital About 40 pages are devoted to this analysis The pathology of the reticulo-endothelial system, general systemic pathology, and pathology of the central nervous system are discussed under separate headings The interesting work of Burrows on the reticulo-endothelial system in poliomyelitis has been more or less corroborated in the authors' series They agree to "the initial restriction of the infection to the reticulo-endothelial system" The pathological changes in the nervous system are discussed in detail with ample illustrations

The epidemiology of the disease is fully covered Such factors as geographic distribution, climate, incidence, effect of season, and the current theories concerning the modes of dissemination are briefly described

The chapters on symptomatology, paralysis, laboratory aids, and diagnosis are amplified with valuable illustrative cases The treatment of the disease is discussed at length All methods currently employed are critically analyzed The opinion of the authors is that serum therapy is of little or no value in preventing paralysis The consensus of opinion both for and against serum therapy, however, is discussed The last chapter gives a valuable short outline on the after care of paralysis, and was written by an orthopedist, Dr Garry de N Hough A short appendix concludes the book There is an ample bibliography at the end of each chapter, covering 236 titles

This book can be highly recommended to anyone desiring a concise, authoritative source of information concerning poliomyelitis

J G A, Jr

Recent Advances in Allergy By GEORGE W BRAY, M B, Ch M, M R C P v + 503 pages, 14 5 × 20 5 cm P Blakiston's Son and Co, Inc, Philadelphia 1934

The title "Recent Advances in Allergy" applied to this work to make it uniform with the other members of the "Recent Advances" series, does not express its completeness, as it presents a good general historical review of the study of allergic disease The author states that his aim is "to provide in a handy and inexpensive form a resume of our present state of knowledge and the trend of modern research in allergy in general, and its individual manifestations in particular"

The book is divided into two parts, the first discussing the nature of hypersensitiveness, the mechanisms of its manifestations in animals and man, and the general factors involved in allergic diseases The second division takes up the individual manifestations of allergy asthma, hayfever, allergic rhinitis, skin diseases, cerebral and gastrointestinal symptoms, bacterial, physical and drug allergies, serum reactions, and hypersensitiveness to animal parasites, fungi, and insects

The most serious adverse criticism that might be advanced is that the author, in the more practical parts of the book, has written specifically for the English, rather

than the American, practitioner In such a subject, the geographic distribution of offending plants, with their pollinating periods, is of prime importance, and American flora have been largely neglected The author states that he has made no effort to present this phase of the subject due to its excellent study in American publications

In general, "Recent Advances in Allergy" is quite complete, very well documented, and, with the above exception, practical It should provide a useful and interesting general view of the subject

T N C

Diseases of the Thyroid Gland By ARTHUR E. HERTZLER, M D 348 pages, 17 × 25 cm C V Mosby Co, St Louis 1935 Price, \$7 50

This monograph is described by its author as an expression of his own experiences and impressions in dealing with affections of the thyroid gland The background is further described as a small country hospital whose isolation makes the investigators more free to follow their own ideas uninfluenced by the opinion of associates It is, therefore, not intended to be either complete or authoritative, and what is lost in encyclopedic quality is gained in freshness, originality and interest

There are disadvantages in this approach to the subject Opinions may be confused with accepted facts, and important recent contributions seem to have limited acceptance by the author The author, for example, is disinclined to use the classification of the Society for the Study of Goiter, yet much of his discussion elsewhere is argument for this same classification, and his reasons cited for non-acceptance apply nearly as aptly to his own classification

One may differ with many statements and conclusions, but this difference of opinion is stimulating, and reminds us that many convictions are, after all, only opinions which may be weakened or strengthened by a good argument

It is to be regretted that one's enjoyment of the book is somewhat marred by occasional lapses from acceptable English

In spite of certain handicaps the book will be keenly enjoyed by all those interested in diseases of the thyroid gland

E M H, JR

Objective and Experimental Psychiatry By D EWEEN CAMERON 271 pages, 15 × 22 cm Macmillan Co, New York 1935 Price, \$3 00

Feeling a "growing distrust of purely descriptive and intuitive concepts of human behavior" and finding it "more and more difficult to content (himself) with facts or assertions save where they will withstand experimentation and will not fail us on prediction," Dr Cameron points out some of the pitfalls of our usual psychiatric records He begins by sketching the development of science in general, from a collection of animistic myths to a more or less precise array of formulae buttressed by objectively demonstrable facts, and stresses the need for a study of human behavior from a more detached point of view, affording more demonstrable behavior items in the patient and less injection of the observer's own personality traits Observational errors, projectionism ("the attempt to ascribe to the patient the feelings and thinking which we consider from our experience he should be entertaining on being exposed to a given situation") and conventionalization (the tendency to make the history of the reaction conform with already delineated concepts) are the greatest defects This thesis, and possible points of attack for experimental methods, are developed in the first two chapters

The next 15 chapters survey impartially the literature on Tests of Intelligence, Introversion—Extraversion, Word Association Tests Conditional Reflexes; Heredity, Statistics Blood Sugar Tests, Response to Ephedrin and Adrenalin, Hemoclastic Crisis, Respiratory Center and Schizophrenia, Epilepsy, Basal Metabolism,

Blood Pressure, Sedimentation Rate Hemo-Encephalic Barrier and pH Relations to Personality, Constitution, and Pathology, in their relation to the problems of abnormal behavior

The field is thoroughly covered, with references from 300 odd writers on the various subjects. The final chapter is a brief presentation of simple statistical methods. It is a well written book of value to psychiatrists because of the validity of the writer's views and the assembled review of material, and to other physicians who may be interested in current experimentation on the objective aspects of personality.

H M M

Russell A Hibbs By GEORGE M GOODWIN 136 pages, 15 × 22 cm Columbia University Press, New York, N Y 1935 Price, \$2.00

Everyone who had the good fortune to know Dr Hibbs will realize how well the author of this treatise has portrayed his character.

Dr Hibbs was a most striking figure at all times, he spoke with a decisiveness that carried conviction, not only by reason of his deep voice and strong face, but also because he would "back-up" his statements with figures that carried authority. He was keenly interested in developing young surgeons and was always ready to offer counsel, to open pathways for advancement, and to stick by his man, he was a stimulating personality by example as well as by suggestion. Only a very few knew Dr Hibbs in his lighter moments and it is gratifying to know that he had some real fun from extra-curricular activities, as he was usually seen working hard, early and late.

Some of the original surgical procedures that Dr Hibbs instituted have become standard throughout the world and have revolutionized the treatment of certain conditions. Thousands of patients are indebted to him for these contributions to surgery as well as to his own personal efforts for them, as individuals.

The New York Orthopedic Hospital with its Country Branch is a lasting monument to Dr Hibbs and will forever bear witness to his indomitable spirit, wisdom, foresight, perseverance and capability.

The author has written about Dr Hibbs in a style which flows easily and which gives a clear impression of the striking personality about whom he is writing.

The collection of original papers in the appendix makes the book valuable also as a reference book, and it might well be added to any surgeon's library. The two tributes preceding the appendix express the feelings of the many who have come into intimate contact with this outstanding orthopedic surgeon.

A F V

Synopsis of Regional Anatomy By T B JOHNSTON, M B, Ch B, Professor of Anatomy, University of London, Guy's Hospital Medical School 3rd Edition Lea and Febiger, Philadelphia 1935 Price, \$4.50

This book is intended to be used side by side with prepared or recently-dissected specimens, and presupposes a fairly accurate knowledge of each region described. Written in concise but distinctly readable form it gives one the impression of a dissecting manual from which the technical instruction and minute detail have been omitted. Added are occasional practical points which serve to stimulate the student's interest in an otherwise rather abstract study.

Except for that part devoted to the central nervous system it is devoid of illustrations, an acceptable omission in a book of this type, especially as mental pictures are best created from the dissected cadaver itself.

The nomenclature is the English adaptation of the B N A, eliminating many of the flaws of the previously-used English terminology and including many new self-

explanatory terms which should with few exceptions find their way into the fuller textbooks. Proper names have been properly excluded.

This book is especially for the student of gross anatomy. It is not a practitioner's book of reference. Put to the purpose for which it is intended it will be a useful adjunct to the student's other books of anatomical instruction.

M R

Diseases of the Mouth and Their Treatment. By HERMAN PRINZ, M D, and SIGMUND S GREENBAUM, M D. xiv + 602 pages, 16 X 24 cm. Lea and Febiger, Philadelphia. 1935. Price, \$9.00.

This is a well written and splendidly arranged text dealing with oral disease. The introductory chapters give a comprehensive description of the embryology, anatomy and physiology of the oral cavity. Mouth examination is described, including clinical, roentgenographic and microscopic methods. Oral hygiene and dental prophylaxis are discussed.

Oral manifestations of local origin, as well as those due to metabolic disturbances, blood dyscrasias, avitaminoses, endocrine diseases, infectious diseases, tropical diseases, parasites, skin diseases, drug eruptions, etc. are all well classified, and described in a systematic and thorough manner. Congenital anomalies, and acquired diseases of the tongue, lips, cheek, palate, salivary glands and floor of the mouth receive adequate consideration. There is a comprehensive classification and description of oral tumors and cysts with methods of diagnosis and treatment.

There is also an interesting discussion of the oral manifestations in functional and organic neurologic conditions: dysarthria, tics, local paralyses, neuralgias, etc.

The closing chapter concerns therapeutic suggestions, such as mouth washes, tooth pastes, ointments and anesthetics.

The book throughout is profusely illustrated with photographs and colored drawings. The method of approach, the completeness of description, and wide range of references make this book authoritative in its field.

B M D

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members

- Dr Clifford J Barboika (Fellow), Chicago, Ill —1 book, second edition, "Treatment by Diet",
Dr Karl E Kassowitz (Fellow), Milwaukee, Wis —1 book, "Around A World On Fire",
Dr David Riesman (Fellow), Philadelphia, Pa, 1 book, "Medicine in the Middle Ages",
New York Homeopathic Medical College, 1 book, "Collected Papers of the New York Homeopathic Medical College and Flower Hospital," containing publications by several members of the College,
Dr John L Goforth (Fellow), Dallas, Tex —1 reprint,
Dr George C Griffith (Fellow), Philadelphia, Pa —1 reprint
Dr M B Marcellus (Fellow), San Francisco, Calif —1 reprint,
Lt Col S U Marietta (Fellow), M C, U S Army—6 reprints,
Dr Ellen C Potter (Fellow), Trenton, N J —2 reprints,
Dr William B Rawls (Fellow), New York, N Y —5 reprints,
Dr Charles F Tenney (Fellow), New York, N Y —1 reprint
-

STATE MEETINGS OF COLLEGE MEMBERS

Connecticut

The first meeting of the Connecticut members of the American College of Physicians was held at the Hartford Hospital, Hartford, Conn, on October 12, 1935. The meeting was held under the chairmanship of Dr Henry F Stoll, Governor of the College for the State of Connecticut. Fifty members of the College were in attendance, as were also the College Governors for the New England States, including New Hampshire, Maine, Massachusetts and Rhode Island, and also Dr James Alex Miller of New York City, President of the College. A program of clinics was given at the Hartford Hospital, beginning at 11 a m and lasting until 4 30 p m. Dr James H Means, Regent of the College from Boston, conducted a clinical pathological conference in the morning, and Dr A M Burgess, Governor for Rhode Island, conducted a similar conference in the afternoon. The social aspects of the meeting included a luncheon through the courtesy of the Avery Convalescent Hospital, a tea through the courtesy of the Neuro-Psychiatric Institute and Hospital and a dinner at the Hartford Club. Dr O G Kiedman was toastmaster at the dinner. Dr James Alex Miller, President of the College, delivered an address on College affairs, and Dr Louis Casamajor of New York City delivered an address on "Interesting Types of Psychoneuroses Met with During the Current Industrial Depression". The meeting as a whole was one of the most successful ones that has been conducted on behalf of the College.

Virginia

During the Virginia State Medical meeting held in Norfolk, October 15 to 17, a dinner was held with 33 Virginia members of the American College of Physicians present at the Monticello Hotel, for the purpose of organizing a more consolidated

unit of the Virginia members of the American College of Physicians. At this meeting Dr J Morrison Hutcheson, Governor of the College for Virginia, was elected President and Dr Frederick C Rinker of Norfolk was elected Secretary. During the meeting a motion was carried appointing a committee of three, including the President and Secretary, to formulate plans to be presented next autumn at a similar dinner during the state medical meeting.

Members of the Medical Club of Philadelphia and graduates of the University of Pennsylvania recently honored one of the distinguished members of the American College of Physicians, Major General Charles Ransom Reynolds, who has recently been raised to the highest rank, that of the Surgeon General, in the medical service of the U S Army. General Reynolds graduated from the University of Pennsylvania School of Medicine in 1899, and has been in the Medical Corps of the U S Army for 34 years, being promoted to his present post last June, when he succeeded Major General Robert U Patterson, who is also a Fellow of this College. General Reynolds will be responsible for the health and welfare of the men of the Army wherever stationed and also for the youths of the CCC who have come under the care of the Army. General Reynolds was born in Elmira, N Y, in 1877, receiving his medical degree at the age of 22, and interned at "Blockley," the Philadelphia General Hospital. Shortly after entering the Army, he went to the Philippine Islands, where he participated in several battles. After returning to the United States for a short period, he returned to the Philippines again, where he won the Silver Star for gallantry in action in aiding the wounded in a battle on the Island of Jolo. At the opening of the World War he advanced to the rank of Lieutenant Colonel. He went overseas as Division Surgeon of the 77th Division of the American Expeditionary Forces, and participated in the offensives at Aisne-Marne, St Mihiel and Meuse-Argonne. He was awarded the Distinguished Service Medal for his service in the field and hospitals. Since the war, he was in charge of the School of Instruction at Carlisle Barracks, in Pennsylvania.

General Reynolds' first assistant in the Surgeon General's office is another Fellow of the College, Brigadier General Matthew A DeLaney, also a graduate of the University of Pennsylvania School of Medicine, Class of 1898. General DeLaney also has a distinguished record in the Army, having served in the Philippine Islands, on the Mexican border and in the World War. He was decorated by the Prince of Wales and cited for gallant and distinguished service by Field Marshal Haig. His entire professional career has been devoted to the Army, except for a few years during the Taft administration when he was the White House physician.

Dr John N Simpson (Fellow and Governor of the College for West Virginia), Morgantown, W Va, has been made Dean Emeritus of the West Virginia University School of Medicine.

Dr D O N Lindberg (Fellow), medical director and superintendent of the Macon County Tuberculosis Sanatorium, Decatur, Ill, has been reelected (third term) as Secretary of the Mississippi Valley Sanatorium Association for 1935-36.

The New York Academy of Medicine is conducting its tenth series of Friday afternoon lectures, starting at 4 30 o'clock. The following Fellows are participating: November 15 Dr Thomas T Mackie, Research Associate, Cornell University

Medical College "The Diagnosis and Treatment of Intestinal Infections Occurring in New York City",

November 22 Dr Emanuel Libman, Consulting Physician, The Mount Sinai Hospital "Points in Medical Diagnosis",

December 20 Dr Ralph Pemberton, Professor of Medicine, Graduate School of Medicine, University of Pennsylvania "The Present Status of Arthritis and the Treatment of It",

January 3 Dr Harlow Brooks, Attending Physician, Bellevue Hospital "Evaluation of Focal Infections from the Internist's Viewpoint",

January 10 Dr A S Blumgarten, Associate Attending Physician, Lenox Hill Hospital "Recent Advances in Endocrine Research and Their Value in Clinical Practice",

March 6 Dr Irving S Wright, Chief of the Vascular Clinic, New York Post-Graduate Hospital "Diagnosis and Treatment of Peripheral Vascular Disease"

The following Fellows of the College were appointed by the Department of State of the United States as delegates to the International Congress on Gastro-Enterology, held in Brussels, Belgium, during last August

Dr Henry L Bockus, Philadelphia, Dr Russell S Boles, Philadelphia, Dr Max Einhorn, New York, Dr Sara M Jordan, Boston, Dr B B Vincent Lyon, Philadelphia, Dr William Gerry Morgan, Washington, D C, and Dr Franklin W White, Boston. Among other members of the College who were present at the Congress were Dr Samuel Weiss (Fellow) and Dr Anthony Bassler (Fellow), New York, Dr William A Swalm (Fellow) and Dr Harry M Eberhard (Associate), Philadelphia. The 1937 Congress will be held in Paris

Dr David P Bair (Fellow), St Louis, was appointed during September to membership on the Council on Pharmacy and Chemistry of the American Medical Association. Dr A J Carlson (Fellow), Dr G W McCoy (Fellow), Dr A C Ivy (Fellow) and Dr William J Kerr (Fellow) are members of the Committee for the Protection of Medical Research of the American Medical Association

Dr Willard R Wirth (Associate) has been appointed assistant professor of medicine at the Graduate School of Medicine, Tulane University of Louisiana

Dr Dwight O'Hara, professor of preventive medicine, Tufts College Medical School, Boston, has been appointed by Governor Curley of Massachusetts as a member of a public health commission to codify the health laws of the State of Massachusetts, eliminating those which are obsolete and revising others

The Medical Society of Virginia held its sixty-sixth Annual Session at Norfolk, October 15 to 17, under the presidency of Dr Francis H Smith (Fellow), Abingdon. Dr Arthur C Christie (Fellow), Washington, D C, and Dr James E Paullin (Fellow and Regent), Atlanta, Ga, were the two guest speakers, whose subjects were "The Answer of the Medical Profession to State Medicine" and "The Significance and Diagnostic Importance of Pain in Disease," respectively. Dr J Morrison

Hutcheson (Fellow and Governor for Virginia) was elected President-Elect and Dr C Lydon Harrell (Fellow), Norfolk, was elected one of the Vice-Presidents Dr Walter B Martin (Fellow), Norfolk, was elected a delegate to the American Medical Association

Dr Hugh S Cumming (Fellow), Surgeon General of the U S Public Health Service, recently gave the dedicatory address of the newly opened isolation pavilion of the Gallinger Municipal Hospital in Washington, D C

Dr Alfred Stengel (Master), Professor of Medicine and Vice-President of the University of Pennsylvania, and Dr Paul Dudley White (Fellow), Assistant Professor of Medicine at Harvard University Medical School, were the two invited guests on the occasion of the second annual Postgraduate Day of the Medical Institute of the University of Toledo, November 8, on the subject of cardiovascular renal disease

Dr George R Maxwell (Fellow), Morgantown, has been reelected President of the West Virginia Tuberculosis Association for 1935-36

Dr Benjamin H Orndoff (Fellow), Chicago, is the general secretary for the fifth International Congress of Radiology, to be held in Chicago during September, 1937

Dr Bernard T McGhie (Fellow), Toronto, is acting deputy minister of health of the division of hospitals and the department of health of Ontario

At the opening exercises of the University of Michigan Medical School at Ann Arbor, Dr Andrew P Biddle (Fellow), Detroit, was the recipient of the honorary degree of Master of Arts, "in recognition of a life devoted to the advancement of education and ethics in the medical profession"

Dr Lowell S Selling (Associate), Detroit, has been appointed psychiatrist in the recorder's court of Detroit, to succeed Dr Isaac L Polozker (Fellow), deceased

Dr Wilham J Stapleton (Fellow), Detroit, has been appointed acting Dean of the Wayne University College of Medicine

Dr Joseph F Bredeck (Fellow), St Louis, is President of the Missouri Public Health Association

Dr Arthur Jackson Patek (Fellow), Milwaukee, founder and for several years editor of the *Wisconsin Medical Journal*, was the recipient of an award for distinguished service by the State Medical Society of Wisconsin at its annual session during

the past autumn Dr Patek is a former president of the Medical Society of Milwaukee County and also of the State Medical Society of Wisconsin

Dr Charles M Griffith (Fellow), Washington, D C, has been elected President of the Association of Military Surgeons of the United States

Dr Roscoe L Sensenich (Fellow), South Bend, has been installed as President of the Indiana State Medical Association for 1936

Dr Edwin W Gehring (Fellow and Governor for Maine) has been named editor of the *Maine Medical Journal*

Dr David P Barr (Fellow), St Louis, has been chosen as a representative of the St Louis Medical Society on the newly created Medical-Dental Service Bureau

A new building for the care of acute cases at the Suffolk Sanatorium, Holtsville, N Y, has been named for Dr William H Ross (Fellow), first president of the county board of health

Dr Ralph R Hendershott (Associate), Tiffin, Ohio, was installed as President of the Ohio State Medical Association at its annual meeting in Cincinnati during October

Dr David Riesman (Fellow), Philadelphia, was installed as President of the Inter-State Postgraduate Medical Association at its annual session in Detroit, October 18

Major Raymond O Dart (Fellow), Washington, D C, is acting curator of the Army Medical Museum, succeeding Major Virgil H Cornell (Fellow)

Dr Wallace M Yater (Fellow and Governor for the District of Columbia) is President of the Washington Society of Pathologists

Dr C C Carpenter (Fellow), professor of pathology at Wake Forest (N C) College of Medicine, has been appointed assistant dean of the College

Dr Nathaniel B Heyward (Associate), Columbia, S C, has been appointed a member of the State Board of Medical Examiners for a four-year term

OBITUARIES

DR AUGUST CAILLÉ

Dr August Caille (Fellow), New York City, died October 10, 1935, of cerebral hemorrhage at the Lenox Hill Hospital, aged, 81 years

Dr Caillé was born in Madison, Indiana, attended the New York College of Pharmacy, graduating in 1873 with highest honors, and then went abroad for the study of medicine at the University of Wurzburg, where he graduated in 1877 Dr Caillé then returned to America and established himself in the private practice of medicine in New York City, in 1879 He resolved to take an American degree in medicine and enrolled in the College of Physicians and Surgeons of Columbia University, and in 1881 received the degree of medicine from that institution

Dr Caillé pursued the study and practice of medicine with much ability and enthusiasm, and was indefatigable in research, especially in the line of children's diseases, on which subject he had become a recognized authority He was appointed Professor of Medicine and Children's Diseases at the New York Post-Graduate Medical School and Hospital in 1888, an appointment he held for nearly fifty years At the time of his death, he was Emeritus Professor of Medicine and Pediatrics and Consulting Physician to the Babies' Wards of the New York Post-Graduate Medical School and Hospital, Consulting Physician to the Lenox Hill Hospital, the Sea Cliff Convalescent Home for Babies and Isabella Home His connections with the Lenox Hill Hospital and the Isabella Home endured for over fifty years

In the proceedings of many important medical bodies, Dr Caille's name appears prominently, for he was elected to many responsible offices He was an ex-President of the American Pediatric Society, a member of his county medical society, the New York State Medical Society and a Fellow of the American Medical Association, in addition to being an honorary member of the German Medical Society in New York City In the earliest annals of the American College of Physicians, Dr Caille's name appears as a member of its Council It is further disclosed that he was elected the second Treasurer of the College at the end of 1916, serving for some years thereafter

Dr Caille was deputed as the American delegate to the International Medical Congress in Berlin He substantially contributed to the medical literature of this country, having published many articles and monographs, the majority of which appeared in leading medical periodicals He introduced Soxhlet's home sterilization of milk and bottle food for infants to the American profession in 1887 He was one of the first in this country to practice and teach spinal puncture and stomach washing He gave the first demonstration of O'Dwyer's method of intubation for croup in Germany at Frankfort in 1887 He devised a perforated trocar for abdominal puncture and an automatic tracheal retractor for facilitating tracheotomy for

membranous croup. He suggested permanent drainage for certain forms of dropsy, and devised a scratch test for the detection of individuals sensitized to animal sera.

He was the author of a comprehensive work on "Differential Diagnosis and Treatment of Disease," published in 1906, and also of a presentation of postgraduate teaching entitled, "Prevention and Treatment of Disease."

DR. PEDRO GUTIERREZ IGARAVIDEZ

Dr. Pedro Gutierrez Igaravidez (Fellow), San Juan, Puerto Rico, died May 24, 1935, aged, 64 years.

Dr. Igaravidez was born in San Juan, Puerto Rico, August 24, 1871. He held the degree of Bachelor of Arts from the Instituto Civil, the degree of Bachelor of Science from the Instituto Ensenanza, Cadiz, Spain, and his medical degree from the University of Sevilla, Spain, 1896. He was formerly Visiting Physician to the Municipal Hospital of San Juan, Medical Director of the Anti-tuberculosis Sanatorium and Member of the Anemia Commission (1904), Chairman of the Puerto Rico Anemia Commission, 1906-10, Director of the Tropical and Transmissible Diseases Service of Puerto Rico, 1910-12, Director of the Institute of Tropical Medicine and Hygiene and Chief of the Laboratory Service of the U. S. Base Hospital in San Juan. He had done postgraduate work at the Polyclinic Hospital of Philadelphia and at the London School of Tropical Medicine in England. He was the author of many published papers.

Dr. Igaravidez was a member of the Royal Society of Tropical Medicine, London, American Society of Tropical Medicine, American Medical Association, American Public Health Association, National Tuberculosis Association, Puerto Rico Medical Association, and had been a Fellow of the American College of Physicians since 1924. He was formerly Clinical Professor of Tropical Medicine in the School of Tropical Medicine of Puerto Rico, conducted under the auspices of Columbia University. At the time of his death, he was Chief of the Division of Roentgenology of the Puerto Rico Department of Health.

Dr. Igaravidez was one of the most prominent clinicians of Puerto Rico and for many years was a close friend and associate of the late Dr. Bailey K. Ashford.

DR. MORGAN SMITH

In the death of Morgan Smith, September 14, 1935, the State of Arkansas lost not only an outstanding leader of the medical profession, but a man who had devoted a large part of his time to the public advancement. Although a general practitioner, Dr. Smith gained his reputation in the field of pediatrics and had done much to further this branch of medicine in the state.

A graduate of the medical departments of the University of Arkansas and Tulane, he began his practice in Little Rock in 1904. Shortly thereafter, Dr. Smith became the state director of the Rockefeller Sanitary Commission for the eradication of hookworm in the South. Out of this commission evolved the Arkansas State Board of Health, and Dr. Smith was its first superintendent.

In 1913, he was appointed Dean of the medical department of the state university and held this position until 1927 when he resigned to resume his private practice. It was under Dr. Smith's regime that the school attained its Grade "A" rating. The pediatric instruction was under his supervision from the time of its introduction in the school until his resignation. He was a member of the American Academy of Pediatrics.

During his lifetime, Dr. Smith had many honors accorded him. He was a past president of the Arkansas Medical Association. He had served on the Council of the Southern Medical Association, and at the time of his death, he was the president of the Arkansas Pediatric Society. He was a Fellow of the College since 1928.

Entering politics in 1929, Dr. Smith was elected to the Arkansas State Senate, and was returned to his seat there for the two following sessions of that body. It was while in the Legislature that he sponsored the Basic Science Law which is now active in medical licensure in Arkansas.

The last two years of his life were spent chiefly at his country home not far from Little Rock. His health had been impaired by cardiac disease, but he was still able to enjoy his many friends and to work among his flowers and vegetables. Death came suddenly as he was enjoying his favorite avocation, reading.

A man of imposing personal appearance, jovial disposition, attractive personality, a peerless raconteur, a skillful and sympathetic physician and a true friend, Morgan Smith made a lasting imprint on the pages of Arkansas medicine.

OLIVER C. MELSON, M.D., F.A.C.P.,
Governor for Arkansas

DR. HARRY WARDWELL CAREY

Dr. Harry Wardwell Carey (Fellow), Troy, New York, died August 14, 1935, of coronary thrombosis, aged 60 years.

Dr. Carey was born in Stamford, Conn., April 15, 1875. He attended the schools of his native State and was graduated from Yale University with the degree of Bachelor of Arts in 1897 and from Johns Hopkins University School of Medicine with the degree of Doctor of Medicine in 1901. He became assistant bacteriologist and assistant pathologist to the Bender Laboratory for a period of two years. He pursued postgraduate study in dermatology at the University of Munich and at the University of Berlin during 1903, returning to Troy to engage in private practice and to act as

instructor in histology at the Albany Medical College In 1904 he became instructor in surgical pathology and in 1905 instructor in physical diagnosis He was pathologist to the Samaritan Hospital from 1904 to 1930, he organized the Society for the Relief of Tuberculosis in 1907, he was bacteriologist for the City of Troy from 1907 to 1926, physician-in-charge of the Lakeview Sanatorium, 1912 to 1916, director of the Social Hygiene Clinic (municipal) from 1919 to 1931, pathologist to the Troy Hospital, 1925 to 1927, and to the Cohoes Hospital from 1927 to 1930 He was attending physician to the Samaritan Hospital from 1930 to the time of his death As a matter of fact, his death occurred while he was making his rounds at the Samaritan Hospital

Dr Carey was a member of the Rensselaer County Medical Society and the New York State Medical Society He was a Fellow of the American College of Physicians since 1931, and a Fellow of the American Medical Association He was the author of many published articles and of a book entitled "Bacteriology for Nurses"

Dr Carey's whole career was marked by an enthusiastic interest in preventive medicine One of his earliest efforts in Troy was to build up a campaign against tuberculosis He succeeded in establishing an institution for the treatment of tuberculosis and was named its first supervising physician As a result of this, the Pawling Sanitarium was later established It was said that the death rate in Troy from tuberculosis is but a small fraction of that of thirty years ago Dr Carey exerted wide influence in other preventive measures such as cancer control, milk inspection, etc In spite of his varied public activities, he conducted an extensive private practice, until his health compelled him to confine it largely to office and hospital work

ISAAC LOUIS POLOZKER

Isaac Louis Polozker (Fellow) was born in Grodno, Russia, October 24, 1873 At the early age of five he determined to become a physician, being influenced by four uncles—all members of the medical profession In 1889 he came to the United States, completed a course at the City College of New York and then moved to Detroit—graduating from the Detroit College of Medicine in 1897 He returned twice to Europe to study, doing postgraduate work in psychiatry at the University of Vienna

Dr Polozker was early interested in pediatrics and contributed numerous published articles in that specialty Later he became interested in psychiatry and became Psychiatrist to the Recorder's Court, Detroit His long experience in general practice brought to his work in the Psychopathic Clinic a rich equipment of experience, particularly useful in the evaluation of criminality

Dr Polozker was a Professor of Clinical Psychiatry at Wayne University and College of Medicine, Detroit, Psychiatrist at the Eloise Hospital

for Mental Diseases, Director of the Psychopathic Clinic of the Recorder's Court, Neuropsychiatrist at St Mary's Hospital, Member of the Wayne County Medical Society, Detroit Medical Group, Detroit Neurological Society, Michigan State Medical Society, Fellow of the American Medical Association, the American Psychiatric Society, American Teacher's Society and the American College of Physicians

On August 21, 1935, he passed away suddenly with coronary thrombosis. He is survived by his widow, the former Florence Higer, whom he married in 1919

J FRANK KILROY, M D

DR ADOLPH H NAHMAN

Dr Adolph H Nahman (Fellow), San Francisco, Calif, died September 21, 1935, aged 58 years

Dr Nahman was born in Poland, and received his preliminary college education at the University of Warsaw. He then entered Northwestern University Medical School, Chicago, from which he received his medical degree in 1909. After graduation, he went to San Francisco, interned at the Southern Pacific Hospital and thereafter became associated with the Mount Zion Hospital, where he attained the position of senior associate of the medical department and chief of the outpatient department. He was a member of the San Francisco County Medical Society, California Medical Association and the American Medical Association, and had been a Fellow of the American College of Physicians since 1926.

Dr Norman Epstein, in the Bulletin of the San Francisco County Medical Society, has written "A great doctor has passed. A kindly, pleasant, cheerful soul who knew no hours, no creeds, no caste when the sick called. He gave of his remarkable ability and rich store of knowledge to poor and wealthy alike.

Dr Nahman truly typified the family physician. He entered the homes of his patients as a friend and advisor. He thoroughly knew and understood his people and their peculiarities. He personally supervised and attended upon every technical procedure done upon his patients.

As an exponent of the sadly neglected art, bedside medicine, he had no equal. His personal and detailed close observation, combined with comforting and rational therapy based on an alert understanding of every advance in modern medicine, instilled confidence. He spent his life in study and work and attained a perfection in clinical medicine which is rarely reached.

Dr Nahman's interests were not exclusively confined to medicine. His devotion to his family was a prominent feature of his life. He loved music, and his hobbies were photography and gardening. He traveled widely and was much interested in general human affairs. To those who knew him his memory will ever endure."

H LISSER, M D, F A C P,
Governor for northern California

DR EMIL JOSEPH SUSSLIN

Dr Emil Joseph Susslin (Associate), Bridgeport Conn , died July 9, 1935, of subacute bacterial endocarditis , aged, 37 years

Dr Susslin was a graduate of the University of Vermont, 1921 His internship was at the Bridgeport (Conn) Hospital At the time of his death, he was Attending Physician to the Englewood Hospital and Assistant Physician at the Bridgeport Hospital He was a member of the Bridgeport Medical Society, the Fairfield County Medical Society, the Connecticut State Medical Society and the American Medical Association He became an Associate of the American College of Physicians during 1928

ANNALS OF INTERNAL MEDICINE

VOLUME 9

JANUARY, 1936

NUMBER 7

CHEMICAL STUDIES IN MYASTHENIA GRAVIS

By MILDRED ADAMS, PH D, MARSCHELLE H POWER, PH D, and
WALTER M BOOTHBY, M D, F A C P, *Rochester, Minnesota*

PREVIOUS metabolic studies of subjects with myasthenia gravis have dealt chiefly with the inorganic metabolism, particularly that of calcium and magnesium, and with the metabolism of nitrogen, creatine, creatinine, and carbohydrate. The results have been more or less contradictory. Marburg¹ reported a high blood magnesium in one case, but Hellich,² and Hellich and Tessenow³ found that the values for the magnesium of the blood were normal (three cases). Bayha⁴ reported a low blood calcium in one case, in contrast to normal values found by Hellich, Hellich and Tessenow, Marburg, Berglund, Medes and Lohmann⁵ and Reuter.⁶ Laurent and Walther⁷ have recently determined values for the potassium of the plasma of six patients with myasthenia gravis. The values appeared to be rather low, but for several reasons, particularly the fact that normal subjects exhibited similar low values, these writers were not inclined to attach great importance to their observations. Keschner and Strauss⁸ determined the sugar, uric acid, creatinine, urea, nonprotein nitrogen, and cholesterol in the blood of two patients with myasthenia gravis, and the values obtained for all of these constituents were normal. From more detailed studies of the inorganic metabolism, Pemberton,⁹ and Diller and Rosenbloom¹⁰ found negative calcium balances in their cases, and noted that improvement occurred as the result of treatment with calcium lactate. Bookman and Epstein,¹¹ on the other hand, found the calcium balances of their patients to be slightly positive, and that the administration of calcium lactate caused no improvement. In similar studies, Halpern¹² reported a more marked retention of calcium than that observed by Bookman and Epstein. The results of studies of the nitrogen balance in cases of myasthenia gravis have been of a similar nature. Kauffmann¹³ observed a positive nitrogen balance in one subject on a high protein diet during rest and a decrease in this balance as the condition became worse as a result of exercise. Pemberton reported a retention of nitrogen, while Diller and Rosenbloom reported a negative

* Submitted for publication September 6, 1935

From the Section on Clinical Metabolism, The Mayo Clinic, Rochester, Minnesota

nitrogen balance Halpein¹² reported a marked retention of nitrogen and phosphorus, and Bookman and Epstein generally noted a retention of nitrogen, sulphur and phosphorus

The excretion of creatine and creatinine by patients with myasthenia gravis has received considerable attention Berglund, Medes and Lohmann, and Remen¹⁴ reported a definite creatinuria in the cases which they had under observation Williams and Dyke,¹⁵ and Bernhardt and Simpson¹⁶ observed a creatinuria only in cases in which the condition was severe, while in the cases of Hellich and Tessenow, Gibson, Martin and Buell,¹⁷ and McCrudden and Sargent,¹⁸ no creatinuria was present Diller and Rosenbloom found low values for the excretion in the urine of creatinine, uric acid, and neutral sulphur, and suggested that the disease is accompanied by a low endogenous metabolism In addition, Spriggs,¹⁹ Pemberton, and also Bookman and Epstein, reported a low excretion of preformed creatinine On the other hand, the excretion of creatinine by the patients observed by Curschmann,²⁰ and of those studied by Hellich and Tessenow, was reported to be normal It is obviously impossible to draw any definite conclusions from the results reported to date, as to abnormalities in the metabolism of patients with myasthenia gravis

In a series (Boothby's²¹) of 71 cases we have had the opportunity to study carefully the excretion of creatine and creatinine of 35 subjects with myasthenia gravis, both before treatment and after the beginning of treatment with glycine Some of the results have been briefly referred to elsewhere,²² but in connection with a general discussion of the effect of the administration of glycine on the excretion of creatine and creatinine and in the papers dealing essentially with the clinical side of the problem The more comprehensive data concerning the excretion of creatinine and of creatine in myasthenia gravis will be included in this paper, together with several illustrative case histories

In addition, we have obtained data for the concentrations of several constituents of the blood of 10 patients with myasthenia gravis These patients, with one exception, had severe myasthenia gravis The group included four females and six males, and the ages of these patients ranged from 17 to 69 years The results are shown in table 1 It is apparent from these data that there is nothing abnormal in the composition of the blood of this group of patients The values obtained for calcium, magnesium, sodium, potassium, inorganic phosphorus, creatinine, uric acid, amino acid, urea, and sugar were found to be well within normal limits

The results of our studies on the excretion of creatinine and creatine in cases of myasthenia gravis are summarized in table 2 In general, control periods of two to five days, during which glycine was not administered, were obtained, except in a few cases in which the patients were already taking glycine at the time of their admission to the clinic After beginning treatment with glycine, data on the daily excretion of creatine and creatinine for periods of usually three weeks or longer were obtained The daily results

TABLE I

Inorganic and Organic Constituents of the Blood of Patients with Myasthenia Gravis *

Case	Mg per 100 c c									
	Calcium**	Phosphorus**	Magnesium**	Sodium**	Potassium**	Urea N†	Uric Acid†	Creatinine†	Amino Acid N†	Sugar‡
1	11.2	4.2	2.5							
2	10.3		2.2	323	18	15	2.2	1.2	3.1	
3	10.0	4.2	2.1	320	19					
4	10.2	3.0	2.3	330	19	16	2.2	1.1	4.3	90
5	10.4	3.9				12	2.8	1.2		95
6	10.2	3.2	2.2	322	20	15		1.1	4.2	82
7						11	2.9	1.0	3.9	
8	10.0	3.5	2.1	342	20					92
9	10.3	3.5	2.9	323	20	14	2.3	1.2	3.2	79
10	10.0	4.4	2.0	325	20					

* Calcium—Clark-Collip modification of Kramer-Tisdall method

Phosphorus—Fiske and Subbarow method

Sodium—Barber and Kolthoff method as modified by Butler and Tuthill

Urea—Van Slyke and Cullen method

Uric acid, creatinine, amino acid N—methods of Folin

Sugar—Shaffer and Hartman method modified by Shaffer and Somogyi

Magnesium—Modification of method of Denis, using Fiske and Subbarow method to determine P in $MgNH_4PO_4$

Potassium—Kramer-Tisdall method

** Determinations made with serum

† Determinations made with Folin's unlaked-blood filtrate

‡ Folin-Wu filtrate of whole blood

for periods of, usually, seven days were averaged, the range of these averages for the time during which glycine was administered is recorded in the table. Throughout the observations the subjects were allowed to take their customary mixed diets. The constant average daily excretion of creatinine and creatine observed after equilibrium had been established on any one regimen suggests that the influence of the intake of food was approximately constant. A few of the subjects were taking ephedrine before the administration of glycine was started, but the response to the administration of glycine appeared to be much the same in these cases as it was in the cases in which ephedrine was not administered.

It is evident from table 2 that the excretion of creatinine and creatine in the untreated patient is not usually abnormal. As a means of comparing different individuals Shaffer²³ has suggested the use of the creatinine coefficient, that is, the milligrams of creatinine, or preferably creatinine nitrogen, excreted per kilogram of body weight in 24 hours. Shaffer presented data which indicated that the creatinine nitrogen coefficient for normal individuals ranges from 5.4 to 11.7, but believed that if inactive, elderly, or obese individuals were excluded, the limits for normal individuals would be approximately from 7 to 11. The creatinine nitrogen coefficients of our male patients ranged from 4.5 to 9.8. If the first five patients, who were

TABLE II

Creatinine and Creatine Excretion of Subjects with Myasthenia Gravis, before and after Administration of Glycine *

Case	Age of Patient, Years	Weight of Patient, Kg	Glycine Administered Daily, Gm	Average, Gm of N in 24 Hours				Creatinine Coefficient**
				Preformed Creatinine		Creatine		Mg Preformed Creatinine N per Kg of Body Weight, in 24 Hours
				Before	After	Before	After	
Males								
2	56	57	30-40	0.43	0.42-0.44	0.04	0.02-0.05	7.6
3	69	84	40	0.39	0.33-0.46	0.03	0.03-0.08	4.6
4	63	79	30-40	0.62	0.58-0.72	0.02	0.02-0.06	7.8
6	34	59	30	0.50	0.45-0.50	0.10	0.22-0.26	8.4
8	65	73	30-40	0.49	0.53-0.54	0.04	0.03-0.03	6.7
9	37	73	30-40	0.59	0.57-0.66	0.04	0.01-0.08	8.1
10	19	48	30-35	0.47	0.47-0.47	0.02	0.11-0.15	9.7
11	67	112	30		0.50-0.51		0.05-0.06	(4.5)
12	67	114	30		0.53-0.58		0.01-0.07	(4.7)
13	65	130	40	0.72	0.75	0.08	0.14	5.5
14	69†	89	30	0.56	0.56-0.57	0.03	0.03-0.05	6.3
15	30†	84	40		0.51-0.57		0.23-0.33	(6.5)
16	42	74	30	0.49	0.47-0.55	0.02	0.00-0.11	6.6
17	50†	100	30-40	0.66	0.45-0.69	0.03	0.03-0.25	6.6
18	63	69	35		0.49-0.50		0.07-0.14	(7.1)
19	56†	78	30	0.57	0.56-0.59	0.00	0.02-0.03	7.4
20	24†	64-67	30-40	0.53	0.46-0.54	0.04	0.17-0.26	7.9
21	28	66	20-40	0.53	0.56-0.60	0.02	0.02-0.10	8.0
22	33	69	30-40	0.58	0.59-0.72	0.01	0.03-0.11	8.4
23	48	78	30-35	0.67	0.65-0.77	0.02	0.01-0.12	8.6
24	55	68	30	0.59	0.56	0.03	0.09	8.6
25	40	81	20-30	0.73	0.69-0.79	0.02	0.04-0.15	9.0
Females								
1	35	55	10	0.44	0.38-0.44	0.01	0.01-0.05	7.9
5	17	48	10-20	0.33	0.34-0.36	0.00	0.02-0.08	7.0
7	40†	75	20-40	0.43	0.42-0.44	0.17	0.20-0.28	5.7
26	21	51	30	0.26	0.31-0.36	0.04	0.10-0.20	5.1
27	40†	67	20-30	0.36	0.35-0.37	0.02	0.05-0.14	5.4
28	22†	51	30		0.31-0.35		0.08-0.13	(6.1)
29	24	73	30	0.46	0.48	0.03	0.06	6.3
30	24	71	30	0.49	0.42	0.02	0.13	7.0
31	27	59	30	0.42	0.41-0.44	0.11	0.14-0.16	7.0
32	36	54	6	0.39	0.35-0.37	0.04	0.01-0.05	7.3
33	33	51-55	20-30	0.38	0.38-0.41	0.10	0.09-0.16	7.5
34	55	40	27	0.30	0.30-0.32	0.17	0.16-0.22	7.6
35	24	60	30	0.40	0.41-0.41	0.06	0.12-0.15	6.8

* Creatinine was determined by the colorimetric method of Folin. Creatine was converted to creatinine by boiling with picric acid, and determined according to the method of Folin.

** The coefficients for certain subjects who were already receiving glycine, or to whom glycine was administered immediately, appear in parentheses.

† Patients were taking ephedrine before treatment with glycine was started.

all 65 years of age or more, and obese, are excluded from consideration, the coefficients of the remaining patients will be found to vary from 6.6 to 9.7. This range is somewhat lower than that considered normal for active individuals by Shaffer, and would probably have been still lower if the patients had been on a strictly meat-free diet. On the other hand, there was no such striking deviation from the normal, as has been suggested occasionally for this disease, particularly in view of the fact that the patients were forced to be relatively inactive. The creatinine nitrogen coefficients of the female patients varied from 5.1 to 7.9, a range which is somewhat lower than that observed for the male patients. However, the range of the coefficients for normal women has frequently been considered to be lower than that for men, so that our values do not seem to differ strikingly from the normal.

The occurrence of a creatinuria in our patients before treatment with glycine was started was observed less frequently than might be expected from previous reports. In only two of 18 males who were under observation before the administration of glycine was begun was the excretion of creatine nitrogen greater than 0.04 gm per day, and in the other patients the excretion of creatine was at most a questionable trace. There was a greater tendency toward creatinuria among the females than among males, five of the 12 female patients on whom control periods were obtained excreted more than 0.04 gm creatine nitrogen per day. This tendency, as is well recognized, has been frequently noted for normal women. The extent of the creatinuria in the group as a whole showed little correlation with the severity of the disease.

The effect of the administration of glycine on the excretion of creatinine and creatine in cases of myasthenia gravis is shown in table 2. So far as creatinine is concerned, little change usually was observed in the excretion after beginning the administration of glycine. In a few cases a slow, gradual increase in excretion of creatinine occurred, which was accompanied by a definite improvement in the condition of the patient. In many other cases improvement occurred without any change in the excretion of creatinine. In four cases the excretion of creatinine gradually decreased during the administration of glycine, in one of these cases, in which the excretion of creatinine was only slightly reduced, the condition was definitely improved, in the other three cases in which the reduction of excretion of creatinine was more marked, the condition became progressively worse in spite of any type of treatment that could be given. There was, therefore, no clear-cut correlation between the condition of the patients and the changes in excretion of creatinine during the periods in which glycine was administered. In no case was there encountered any abrupt, sudden alteration in the excretion of creatinine.

As regards creatine, the excretion of this substance was almost always increased after the administration of glycine and in several cases it was markedly increased. Harris and Brand,²¹ likewise, observed a slight increase in the creatine excretion in a case of myasthenia gravis in which 22

gm of glycine were administered per day. Milhoi²⁵ also has observed that the administration of glycine in cases of myasthenia gravis may increase an existing creatinuria, or provoke one where none existed previously. Some other investigators, who studied only a few cases,^{3 11 26 27} have failed to note an increase in the excretion of creatine following the administration of glycine. We have found that the type of change in the excretion of creatine incident to the administration of glycine may vary considerably. Some subjects exhibited an immediate and marked increase in the excretion of creatine, others responded more slowly and gradually, while still others exhibited no response. Because of the slow rate of change observed for many of the subjects, it seems likely that the few who were in this last group would have exhibited some change if they had been under observation for a longer period.

The following reports of cases illustrate these points in somewhat greater detail than the data in table 2.

CASE REPORTS

Case 9. A man, aged 37 years, who weighed 73.1 kg and whose height was 5 feet and 7 inches (170.2 cm), had had myasthenia gravis for four months before he registered at the clinic. He had not received any treatment during this period. There was marked weakness of the muscles of the arms, legs, neck, and eyelids, and of the muscles of mastication and deglutition. The patient was so weak that he could barely walk one block, even with help. Improvement, which occurred after the administration of glycine, was approximately 25 per cent in the first two weeks, and approximately 50 per cent at the end of six weeks. At the end of three or four months his condition was still further improved. This improvement has been maintained, and during the last year medication has not been required. He now has been employed at full-time work on the railroad for more than a year. This is the only patient in this series of cases who apparently has been able to maintain his strength completely after medication has been discontinued. The effect of the administration of glycine on the excretion of creatinine and creatine by this patient is shown in table 3. It may be noted that a small but definite increase in the excretion of both

TABLE III

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Days in period	2	7	7	7	7	7	8	8	8	10	6	13	8
Preformed creatinine nitrogen, gm	0.59	0.62	0.60	0.59	0.58	0.57	0.57	0.66	0.63	0.62	0.65	0.64	0.67
Creatine nitrogen, gm	0.04	0.02	0.03	0.01	0.03	0.03	0.04	0.03	0.08	0.07	0.07	0.06	0.03
Glycine, gm administered per day	0	30	30	30	30	30	30	30	40	40	40	40	40
Ephedrine, mg administered per day												48	48

* Periods of observation were consecutive.

creatinine and creatine occurred. The decrease in the excretion of creatine in the last period may have been caused by the ephedrine, which was administered during this time.

Case 16 A man, aged 42 years, who weighed 73.9 kg, and whose height was 5 feet and 10½ inches (179 cm), had had myasthenia gravis for three or four weeks before he came to the clinic. The condition had progressed rapidly. There was moderate weakness of the muscles of the arms and legs, and of the muscles of mastication and deglutition. He was able to walk several blocks and could eat food without great difficulty. He improved slowly but definitely after the administration of glycine was started, during the two months he remained at the clinic. The daily excretion of creatine increased from a trace to 0.26 gm, and there also was a progressive and definite increase in the daily excretion of preformed creatinine (table 4).

TABLE IV

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*							
	1	2	3	4	5	6	7	8
	2	7	7	7	9	7	7	12
Days in Period								
Preformed creatinine nitrogen, gm	0.49	0.47	0.53	0.55	0.55	0.59	0.61	0.63
Creatine nitrogen, gm	0.02	0.02	0.00	0.05	0.11	0.23	0.26	0.26
Glycine, gm administered per day	0	30	30	30	30	30	30	30
Ephedrine, mg administered per day						16	16	16

* Periods of observation were consecutive.

Further improvement occurred for some time after he left our immediate observation. Then, following a slight relapse, he apparently became discouraged and adopted other treatment. He gradually failed and died about 13 months after he first was seen at the clinic.

Case 25 A man, aged 40 years, who weighed 81.1 kg and whose height was 5 feet and 9¾ inches (177.2 cm), had had myasthenia gravis for four months before he came to the clinic. He had not received any treatment during this period. There was moderate weakness of the muscles of the arms, legs, neck, and eyelids, and of the muscles of mastication and deglutition. He was able to walk fairly well, and before he came to the clinic he had been able to work part of each day as a contractor. Definite improvement occurred after the administration of glycine. The improvement was accelerated by the additional administration of ephedrine. He is back at full-time work at present, two and a half years after he first came to the clinic. It has been possible to reduce the dosage of the glycine somewhat but he notices a weakness when the administration of the drug is discontinued. There was an increase in the excretion of creatine and a slight increase in the excretion of preformed creatinine after the administration of glycine (table 5). The slight decrease in the excretion of creatine observed in periods 6 and 7 may be due to the administration of ephedrine.

Case 20 A man, aged 24 years, who weighed 67 kg and whose height was 5 feet and 8¾ inches (174.6 cm), had had myasthenia gravis for nine years before he came to the clinic. There had been partial remissions during this period. Ephedrine 3/8 gram (0.024 gm), had been administered four times daily for five weeks before he came to the clinic but had not produced any improvement. At the clinic, the

TABLE V

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*						
	1	2	3†	4	5	6‡	7§
Days in Period	2	5	8	7	5	1	1
Preformed creatinine nitrogen, gm	0.73	0.69	0.73	0.73	0.79	0.75	0.82
Creatine nitrogen, gm	0.02	0.04	0.15	0.13	0.14	0.10	0.10
Glycine, gm administered per day	0	20	30	30	30	30	40
Ephedrine, mg administered per day						16	16

* Periods of observation were consecutive unless otherwise stated

† Two weeks after period 2

‡ Two months after period 5

§ Nine months after period 6

administration of ephedrine was reduced to 3/8 grain (0.024 gm) twice daily. A constant intake of food was employed, and food, urine, and feces were analyzed. The nitrogen balance was markedly negative. The additional administration of 15 gm of glycine, twice daily, improved the nitrogen balance only slightly. The excretion of creatine increased rather rapidly after the administration of glycine and maintained a fairly constant level, except in the ten days during which creatine was administered (table 6). The extra creatine given during this time (period 9) was

TABLE VI

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Days in Period	4	7	7	7	3	11	9	11	10	7	9	6	5	7	7	8	7	11	12
Preformed creatinine nitrogen, gm	0.53	0.54	0.51	0.52	0.52	0.52	0.49	0.46	0.47	0.46	0.41	0.43	0.42	0.41	0.41	0.40	0.39	0.39	0.39
Creatine nitrogen, gm	0.04	0.17	0.19	0.19	0.21	0.22	0.23	0.26	0.54	0.27	0.18	0.26	0.30	0.35	0.27	0.24	0.27	0.27	0.29
Glycine, gm administered per day	0	30	30	30	30	40	40	30	30	30	30	30	30	30	30	30	30	30	30
Ephedrine, mg administered per day	48	48	48	48	72	72	48	48	50										
Creatine, gm administered per day †									1										
Doschatein, cc administered per day										5 to 20	5 to 20								

* Periods of observation were consecutive

† One gm of creatine is equivalent to 0.28 gm of nitrogen. The extra creatine was quantitatively excreted.

quantitatively excreted. There was a progressive and marked decrease in the excretion of preformed creatinine. The administration of glycine never produced any consistent or material clinical improvement. The patient could not walk and was barely able to turn over in bed. All of his muscles were very weak and he could not raise his head. There was marked difficulty in swallowing which made it necessary to abandon the balance studies and resort to nasal feeding. During the following

five months there was only slight fluctuation in the clinical condition. He never was able to walk more than 20 or 30 steps. He was troubled greatly with mucus in the pharynx. The administration of insulin or eschatin for short periods did not produce any change in the clinical condition, although there were periods in which the intensity of the condition varied. In July 1935, approximately five months after he came to the clinic, he was able to be out of doors in a wheel chair, but he never regained the ability to swallow. He returned home the same month, where he continued to follow about the same treatment as was employed at the clinic. He caught cold, probably pneumonia developed, and he died in the latter part of September.

The changes in the excretion of creatine which followed the administration of glycine are not necessarily characteristic of myasthenia gravis, as we have obtained similar results in many other conditions, such as chronic fatigability, various types of muscular disturbances, and arthritic and rheumatic-like conditions.²²

Complete balance studies have been obtained in two cases of myasthenia gravis. The detailed results will be reported shortly. In general, the results indicated that the type of balance found depended on the condition of the patient at the time of the investigation. The two patients observed both had very severe myasthenia gravis. Both subjects were taking 3/8 grain (0.024 gm) of ephedrine sulphate, twice daily, when the studies were started and the administration of ephedrine was continued throughout. One subject, although unable to get around to any great extent without the aid of a wheel chair, had been showing a slow, gradual improvement partly as a result of the administration of ephedrine for several years. She was found to be in nitrogen balance before glycine was administered and maintained this balance when 40 gm of glycine per day were administered. Nothing abnormal was seen in the sodium, potassium, calcium, magnesium, phosphorus, or sulphur balances, either before or after the administration of glycine. The other patient, who was becoming rapidly worse in spite of the administration of ephedrine, showed a negative nitrogen balance which was somewhat less negative after the administration of glycine. The addition of 30 gm of glycine (5.6 gm nitrogen) to the diet failed, however, to prevent a steady loss of nitrogen. Slightly negative sulphur, phosphorus, and calcium balances were also observed in this case, both before and after the administration of glycine.

SUMMARY

The results of metabolic investigations on patients with myasthenia gravis show that the blood contains normal amounts of calcium, magnesium, sodium, potassium, phosphorus, sugar, urea, creatinine, amino acids, and uric acid.

Contrary to many previous reports, no striking abnormalities were observed in the excretion of preformed creatinine, or usually in the excretion of creatine. A definite creatinuria, exceeding 0.04 gm daily, was observed in only seven out of 30 cases and the greater proportion of the patients who excreted creatine were women.

The administration of glycine was not followed by any definite, constant, type of change in the excretion of creatinine in the majority of cases. If the excretion of creatinine progressively and markedly decreases, the prognosis may be rather unfavorable. The excretion of creatine subsequent to the administration of glycine was in general appreciably increased.

Balance studies which we have carried out, as well as those of previous investigators, indicate that the condition of the patient determines the type of balance obtained, rather than that any particular abnormality in the metabolism is characteristic of myasthenia gravis.

BIBLIOGRAPHY

- 1 MARBURG, O. Zur Pathogenese der Myasthenie (Mineralstoffwechsel-Thymus), *Wien klin Wchnschr*, 1931, *xiv*, 413-414.
- 2 HELLICH, I. Zur Kenntnis des Mineralstoffwechsels bei Myasthenia pseudoparalytica, *Deutsch Ztschr f Nervenhe*, 1932, *cxxiv*, 239-246.
- 3 HELLICH, I., and TESSENOW, C. Stoffwechseluntersuchungen bei "Myasthenia pseudoparalytica," *Ztschr f d ges Neurol u Psychiat*, 1933, *clvi*, 219-228.
- 4 BAYHA, C H. Myasthenia gravis, *Ohio State Med Jr*, 1931, *xxviii*, 956-958.
- 5 BERGLUND, H, MEDES, G, and LOHMANN, A. The effect of hypercalcemia on the creatin output in myasthenia gravis, *Proc Soc Exper Biol and Med*, 1927, *xxv*, 204-205.
- 6 REUTER, A. Zur Kenntnis der Myasthenia gravis, *Deutsch Ztschr f Nervenhe*, 1931, *cxx*, 131-161.
- 7 LAURENT, L P E, and WALTHER, W W. The influence of large doses of potassium chloride on myasthenia gravis, *Lancet*, 1935, *ccxxviii*, 1434-1435.
- 8 KESCHNER, M, and STRAUSS, I. Myasthenia gravis, *Arch Neurol and Psychiat*, 1927, *xvii*, 337-376.
- 9 PEMBERTON, R. The metabolism of myasthenia gravis, with a suggestion regarding treatment, *Am Jr Med Sci*, 1910, *cxxxix*, 816-821.
- 10 DILLER, T, and ROSENBLUM, J. Metabolism studies in a case of myasthenia gravis, *Am Jr Med Sci*, 1914, *clviii*, 65-76.
- 11 BOOKMAN, A, and EPSTEIN, A A. The metabolism in a case of myasthenia gravis, with considerations on the administration of calcium and of glandular preparations, *Am Jr Med Sci*, 1916, *cli*, 267-274.
- 12 HALPERN. Quoted by Bookman and Epstein.
- 13 KAUFFMANN, M. Stoffwechseluntersuchungen bei einem Fall von myasthenischer Paralyse, *Monatschr f Psychiat u Neurol*, 1906, *xx*, 299-330.
- 14 REMEN, L. Zur Pathogenese und Therapie der Myasthenia gravis pseudoparalytica, *Deutsch Ztschr f Nervenhe*, 1932, *cxxviii*, 66-78.
- 15 WILLIAMS, B W, and DYKE, S C. Observations on creatinuria and glycosuria in myasthenia gravis, *Quart Jr Med*, 1922, *xv*, 269-278.
- 16 BERNHARDT, H, and SIMPSON, S L. Ein Beitrag zur Frage der Beziehung der Nebennierenrinde zum Krankheitsbild der Myasthenia gravis pseudoparalytica, *Klin Wchnschr*, 1932, *vi*, 2069-2071.
- 17 GIBSON, R B, MARTIN, F T, and BUELL, M V R. A metabolic study of progressive pseudohypertrophic muscular dystrophy and other muscular atrophies, *Arch Int Med*, 1922, *xxix*, 82-96.
- 18 MCCRUDDEN, F H, and SARGENT, C S. Chemical changes in the blood and urine in progressive muscular dystrophy, progressive muscular atrophy and myasthenia gravis, *Arch Int Med*, 1918, *xxi*, 252-255.
- 19 SPRIGGS, E I. On the excretion of creatinine and uric acid in some diseases involving the muscles, *Quart Jr Med*, 1907, *i*, 63-87.

- 20 CURSCHMANN, H Beobachtungen und Stoffwechseluntersuchungen bei Myasthenia pseudoparalytica, Deutsch Ztschr f Nervenhe, 1931, cLVII, 67-80
- 21 BOOTHBY, W M Myasthenia gravis (sixth report), ANN INT MED, 1935, I, 143-149
- 22 ADAMS, M, POWER, M H, and BOOTHBY, W M The influence of glycine on the excretion of creatine and creatinine, Am Jr Physiol, 1935, cXI, 596-610
- 23 SHAFER, P The excretion of kreatinin and kreatin in health and disease, Am Jr Physiol, 1908, XLIII, 1-22
- 24 HARRIS, M M, and BRAND, E Metabolic and therapeutic studies in the myopathies with special reference to glycine administration, Jr Am Med Assoc, 1933, cI, 1047-1052
- 25 MILHORAT, A T Effect of glycocoll and ephedrine in myasthenia gravis, Am Jr Physiol, 1934, cIX, 75
- 26 SCHMITT, E O G The use of glycine in the treatment of myasthenia gravis, ANN INT MED, 1934, VII, 948-959
- 27 REUTER, A, and ZIMMERMANN, W Stoffwechseluntersuchungen bei Myasthenie, Ztschr f klin Med, 1933, cXLIV, 99-110

METABOLISM OF CREATINE AND CREATININE IN MUSCLE DISEASE¹

By A T MILHORAT and H G WOLFF, F A C P, *New York, N Y*

1 PATIENTS with diseases which affect the skeletal muscle commonly have a creatinuria even when they are maintained on a creatine-free diet. Accompanying the creatinuria, there is usually a diminution in the excretion of creatinine and in the ability of the body to retain ingested creatine (a low creatine tolerance)

2 In progressive muscular dystrophy, often large amounts of creatine are excreted. The level of the creatinuria and the impairment of the creatine tolerance are usually related to the amount of muscle disability. In advanced stages of the disease the creatine tolerance may be impaired to the extent that all of an ingested dose of creatine is excreted in the urine as creatine. The amounts of creatinine excreted are diminished and appear to be related to the amount of functioning muscle still remaining.

The ingestion of glycine for short periods is followed by an increase in the creatinuria and a further decrease in the creatine tolerance. In fact, under these circumstances, the glycine appears to act as an amplifier of defects in creatine tolerance. Moreover, it is sometimes of use in demonstrating less obvious disturbances in creatine metabolism. Such effects differ markedly and are not to be confused with the results of prolonged ingestion of glycine.

In keeping with the widespread and serious involvement of muscles in the infantile and juvenile forms of progressive muscular dystrophy is the severe disturbance in creatine and creatinine metabolism. Not only is the muscle involvement extensive and the disturbance in metabolism severe, but the march of the defect in muscle function and metabolism is rapid. In contrast, stand those patients in whom the muscle disease appears later in life. The muscular deficiency in these subjects progresses slowly, and the disturbances in the creatine and creatinine metabolism are less. The parallelism between the severity of muscle disease and rapidity of progression of the disturbance in metabolism is probably not coincidental.

3 In most cases of myasthenia gravis, only moderate amounts of creatine are eliminated and the creatine tolerance is only moderately impaired. However, patients in whom the course of the disease progresses rapidly to a fatal termination excrete large amounts of creatine and show a more serious defect in the ability to retain ingested creatine. The diminution in the creatinine output appears to be proportional to the loss in the functional capacity of the muscles. The defect in the creatine tolerance can be exag-

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

From the New York Hospital and the Department of Medicine, Cornell University Medical College and the Russell Sage Institute of Pathology, New York, N Y.

gerated by the ingestion of glycine in patients during an exacerbation of symptoms. Glycine usually has no effect on the creatine tolerance during periods of remission.

4 In amyotonia congenita usually considerable amounts of creatine are excreted. Also, the creatine tolerance is low and the creatinine output is much diminished. Glycine increases the creatinuria and further decreases the creatine tolerance.

5 In myotonia congenita no abnormality in the metabolism of creatine or creatinine could be demonstrated by the methods employed. Like normal subjects, patients with this condition eliminate no creatine or only minimal amounts spontaneously, and are able to retain fairly large amounts of ingested creatine. The amounts of creatinine excreted are similar to those observed in normal individuals of the same weight, sex, and muscular development. Glycine, in the amounts used, is without effect on the excretion or the creatine tolerance.

6 In patients with myotonia atrophica, however, the metabolism of creatine and creatinine is abnormal. There is a diminution in the creatinine excretion which appears to be directly proportional to the reduction in muscle mass. There is spontaneous creatinuria, although the amounts of creatine excreted are much lower than in patients with progressive muscular dystrophy showing similar amounts of muscle disability. In fact, extensive wasting of the muscles and considerable disability of important muscle groups can occur with only a slight or moderate creatinuria. The creatine tolerance is only moderately impaired and is unaffected by the ingestion of glycine. Only in patients showing extreme and extensive involvement of the muscles are large amounts of creatine excreted. The creatine tolerance is then seriously impaired, and the ingestion of glycine is followed by an increase in the creatinuria and a further decrease in the ability to retain ingested creatine. In short, in their metabolism of creatine and creatinine, patients with myotonia atrophica resemble only superficially those with progressive muscular dystrophy.

7 In patients with muscle wasting associated with disease of the anterior horn cells or of the peripheral nerves, the diminution in the creatinine output appears to be directly proportional to the reduction in muscle mass. The amounts of creatine eliminated are smaller than are observed in patients with progressive muscular dystrophy with similar amounts of wasting. Furthermore, the impairment in the creatine tolerance is less than in similarly incapacitated patients with progressive muscular dystrophy. Unless the muscle wasting is extensive, glycine is without effect on the creatinuria or the creatine tolerance. However, when the involvement of the muscles is so extensive as to include most of the skeletal muscles, there may occur defects in the metabolism of creatine and creatinine of a magnitude that equals that seen in advanced stages of progressive muscular dystrophy.

8 The effect of glycine on the metabolism of creatine in muscle disease, as shown in the creatinuria and creatine tolerance, is out of all proportion to the effect of comparable amounts of nitrogen from sources other than glycine and creatine. It is postulated that glycine acts as a precursor of creatine.

9 When creatine is ingested, the absolute amount retained is not fixed but is relative and dependent upon the amount, within fairly wide limits, of creatine administered. The percentage retention, however, is constant. Only when very large amounts are ingested is the amount retained no longer proportional to the amount administered. In these instances, the absolute amounts retained are constant and apparently represent the maximum capacity of the body to hold exogenous creatine.

10 In patients with muscle wasting the total creatinine coefficient (milligrams of creatinine plus creatine per kilogram of body weight) is not constant but diminishes as the incapacity of the muscle advances.

Examination of the data makes it seem probable that a defect in the metabolism of creatine and creatinine may be taken as an index of the total amount of improperly functioning muscle rather than of the amount of wasted muscle. In wasting secondary to cord disease, although certain muscle fibers are completely destroyed by disease, others are perfectly adequate and completely functioning. Moreover, in patients severely affected with wasting subsequent to nerve disease there are commonly regions of the body in which muscle structure and function are adequate and even entirely normal. Under such circumstances clearly evident atrophy may be accompanied by only slightly disturbed creatine and creatinine metabolism. In contrast, primary myopathy may be looked upon as the expression of a general disturbance in the muscle metabolism which affects all or most of the muscle tissue of the body. Furthermore, the actual enlargement of the muscles in certain myopathies, notably progressive muscular dystrophy, makes it especially difficult to correlate visible wasting with the known defects in metabolism. Hence, the necessity is apparent of expressing muscle status in terms of functional capacity rather than of size or postulated structural alterations. It is therefore clear why slight or barely visible atrophy may be accompanied by a severe disturbance in the metabolism of creatine and creatinine.

In brief, in patients affected by a generalized defect in the metabolism of muscle, all of the muscle fibers in the body may be affected chemically without striking visible evidence of wasting until the process has persisted for long periods. On the other hand, patients with striking visible evidence of atrophy may have the bulk of the musculature still in a sound state and hence show minimal evidence of disturbance in metabolism.

Thus, disturbance in creatine and creatinine metabolism and muscle defects are related and sometimes parallel each other. The term muscle

defect does not of necessity imply wasting although this may be present (In fact the muscle may seem enlarged) Moreover, in those instances where disease is widespread, notably in primary myopathic diseases, the most serious disturbances in metabolism occur, whereas in the myelopathic diseases in which the muscular involvement is commonly more circumscribed, the metabolic disturbances are less The exceptions to this general correlation are unusual instances of myelopathic diseases which are so widespread as to simulate the myopathic diseases in their effect on the muscles In brief, there is a parallelism between the metabolic disturbances and the total mass of improperly functioning muscle

EXPERIMENTAL THROMBOPENIC PURPURA, CYTOLOGICAL AND PHYSICAL CHANGES IN THE BLOOD *

By LEANDRO M TOCANTINS,† *Philadelphia, Pennsylvania*

WHEN a moderate dose of antiplatelet serum is given to a dog, the animal develops an attack of purpura hemorrhagica, identical in most respects with the human type, and recovers spontaneously. The changes that accompany such a disease in the dog have not as yet been systematically investigated. The observations here presented are the result of a study of some of these changes in a group of 63 dogs in each one of which purpura was produced one or more times.

EXPERIMENTAL METHODS

Cytology Various methods of counting platelets^{1,2,3} were tried and the direct method was finally selected. With dogs, when blood was obtained from the ear vein, rapidly handled and with the proper precautions, this method proved to be the most satisfactory. After preliminary shaving and cleaning of the area, the vein was cut with a sharp knife, the tip of the pipette placed against the opening in the vein, and from the freely bleeding wound, blood was aspirated into a 1–200 dilution pipette that had been previously filled with the diluting solution to the 0.5 mark. The diluting fluid was made up of brilliant cresyl blue 0.05 gm, sodium citrate 3 gm, formalin (40 per cent) 0.2 c.c., and distilled water 100 c.c., and the platelets were counted with a high power dry objective and 10X ocular (400X) in a Neubauer chamber. The average of two determinations was taken, if no agglutination was present and if the difference between them was not greater than 8 per cent (technical error for the method) of that average, otherwise the count was either repeated or reported as lost. Erythrocytes were counted in the same preparations and with equal precautions (technical error 5 per cent). The relative number of macroplatelets was recorded by designating as such any platelet that exceeded in length the diameter of an erythrocyte. Preliminary filtering and chilling of solutions, the use of chilled, certified pipettes, and automatic shaking were precautions taken with each count, care was taken to keep all glassware and solutions free of dirt, dust and bacterial contamination, blank counts being performed at intervals on the solutions. Observations on the morphology of the platelets, as well as differential erythrocyte and leukocyte counts, were done on blood smears stained with Wright's stain and buffer solution. Platelets were measured

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

† J. Ewing Mears Research Fellow, Department of Medicine, Jefferson Medical College, Philadelphia.

along their greatest diameter by means of a micrometer eyepiece, and note was taken of the presence or absence of hyalomere, the type of granules, and quality of the staining reaction. The absolute number of nucleated erythrocytes per cu mm was calculated from their percentage in the differential white cell count since no difference can be made out between white cells and nucleated red blood cells in a counting chamber. The *bleeding time* was measured in at least three separate locations at each occasion: the ear vein, the skin of the abdomen, and that of the anterior surface of the thigh. The vein was not cut across but simply nicked at one side, the incisions in the abdomen and thigh were approximately 5 mm long and 2 mm deep and were performed by the same operator with a sharp knife after pinching the skin up a little. The edge of a piece of absorbent paper was lightly touched to the surface of the wound at intervals of 15 seconds, or at 30 seconds when the blood was flowing at a slower rate. In all but a few instances, the determination was not continued if it exceeded 25 minutes, being recorded as 25'+. The *mean bleeding time* is the average of at least three simultaneous determinations in separate locations on the same animal. Strictly speaking, its technical error cannot be estimated since each determination involves making a cut in a separate part of the skin, and the location and structure of the skin where the cut is made play a part in the duration of the bleeding. Including such differences, the mean per cent variation between simultaneous determinations performed in normal dogs by the same operator was ± 21.2 per cent, which rendered multiple, simultaneous determinations imperative. The *coagulation time of the blood* was determined by aspirating venous blood into clean, dry, previously boiled syringes and placing 1 cc into each of two clean tubes 8 mm in diameter, paraffin coated. Clean sharp needles of wide bore and short bevels, and only trained animals with large veins were used. The blood was incubated at 37°C ($\pm 1^{\circ}$) and clotting was considered complete when the tubes could be inverted without the contents falling out. If the difference between the time taken by the blood to clot in the two tubes was not greater than 15 per cent of the average of the two, the longer time was considered the clotting time, otherwise the determination was discarded if it could not be repeated. *Retraction of the clot* is expressed in units and was estimated by methods described elsewhere⁴; the blood was placed in an uncoated glass tube 8 mm in diameter, a uniform amount always used (1 cc) and the clot observed and measured $\frac{1}{2}$, 1, 2, 24, and 48 hours after being formed. For the determination of the *petechiae reaction of the skin* an automatic device was employed that produced a graded amount of trauma to the skin surface over an area of uniform size. Depending on the number of petechiae brought out five minutes after the trauma was applied, the result was reported as 0, 1, 2, 3, etc.

Whenever indicated, the usual statistical methods were employed^{5,6} in the grouping and analysis of the results. Correlation coefficients were calculated by Pearson's method⁷. For any coefficient that appeared significant,

the correlation *ratio* was also calculated. If there was a *significant* difference between them, the correlation was regarded as non-linear and the ratio taken as its truer measure. A difference was considered significant when it was greater than four times its probable error, as calculated by Blakeman's method⁸. Correlation coefficients and ratios were considered significant when they exceeded six times their respective probable errors. It should be kept in mind that any correlations found do not apply to the whole universe of facts concerning each pair of variables but simply in normal dogs under the specified environmental conditions and at various stages of experimental thrombopenic purpura. Correlations involving the

TABLE I

Numerical Values for the Cytological Constituents of the Blood and the Bleeding Time, Venous Clotting Time and Clot Retraction in Normal Dogs

Determinations	Mean ± P E	Standard Deviation ± P E	Maximum Minimum	Coefficient of Variation	Number of Animals	Number of Deter- minations
Platelets	461,500 ±7,277	141,400 ±5,143	960,000 188,000	30.6%	53	173
Erythrocytes	6,130,000 ±46,884	908,500 ±33,104	9,130,000 4,020,000	14.8%	53	172
Leukocytes	12,287 ±283	5,465 ±202	32,300 3,800	44.4%	53	164
Bleeding time Ear vein (Minutes)	1.54 ±.04	.905 ±.03	6 5	58.7%	52	147
Abdominal skin (Minutes)	1.59 ±.05	.943 ±.03	5.5 5	59.3%	52	130
Skin of thigh (Minutes)	1.48 ±.04	.793 ±.03	4.5 5	53.5%	52	107
Venous clotting time (Minutes)	17.53 ±.364	3.97 ±.25	30 10	22.6%	6	54
Clot retraction (Units)	2.03 ±.02	.29 ±.01	2.5 9	14.4%	6	64

number of platelets, erythrocytes, leukocytes, the mean bleeding time, and the skin petechiae reaction were calculated from a group of 414 pairs of determinations each, those involving the venous clotting time and clot retraction, from 139 pairs. In table 1 are summarized the values for the various determinations in normal, unanesthetized, fasting dogs. The size, breed, and age of the animals, the diet and living conditions have been previously stated⁹. The figures for the platelets and erythrocytes show close agreement with those found by Aynaud¹⁰ on 25 dogs. Only slight differences were found in the platelet content of blood obtained without stasis from vessels

in the different portions of the body (marginal ear veins, right and left jugular, cubital and right femoral veins, right carotid artery)

CYTOLOGICAL CHANGES

Platelets The rapidity of decline in the platelet level after the administration of antiplatelet serum depended on the route employed. Within two to five minutes after an intravenous injection the platelet count was below 50,000 per cu mm, and large masses of clumped lysed platelets appeared in the peripheral blood. After an intraperitoneal injection it took from three to five hours for the platelets to reach a low level (chart 1), subcutaneously,

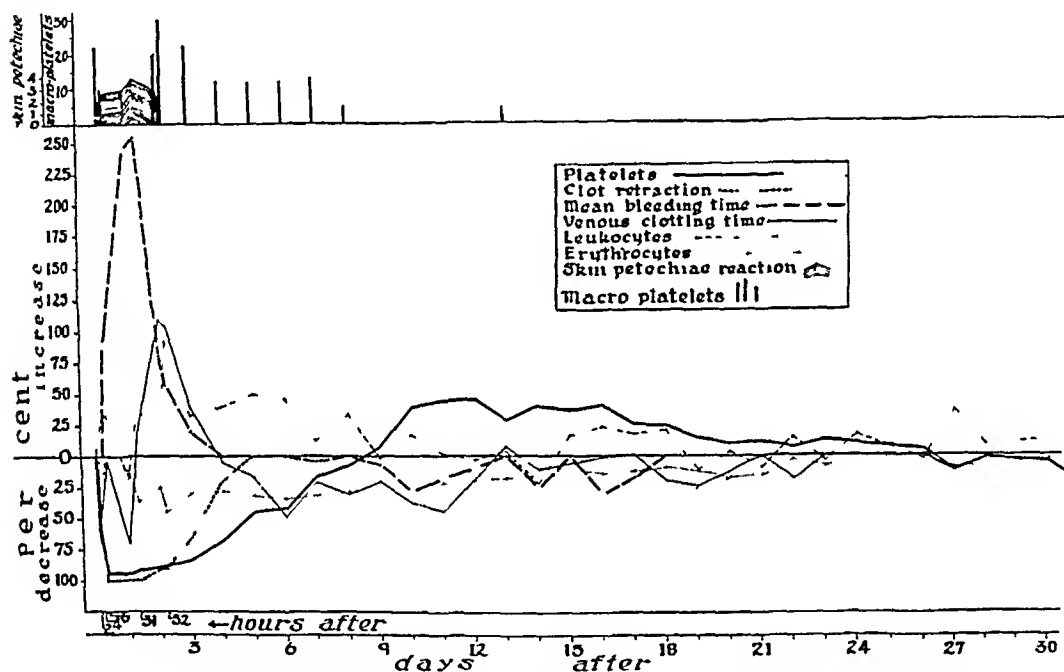


CHART 1 Mean per cent deviations from normal in dogs that received a single intraperitoneal injection of 0.1 cc of antiplatelet serum per kg body weight (The normal range of values for each animal was ascertained, then the per cent deviation from the upper or the lower limit of this range was calculated for every determination performed at stated intervals after the injection. The curves were constructed from the means of all per cent deviations calculated for each period. Number of animals, seventeen. The curves for the clotting time and clot retraction were derived from seven animals only. Macroplatelets and skin petechiae reaction in absolute thousands and degrees, respectively.)

as long as 12 hours. With a moderate dose the thrombopenia usually lasted 48 to 72 hours, but longer in a few animals. One animal remained thrombopenic for seven days following a moderate dose. The promptness of the recovery was also variable. Most animals regained their previous platelet level three to five days after the last day of thrombopenia and then exceeded it for the next two weeks, the peak being reached from eight to twelve days after the last day of thrombopenia (chart 1). After smaller doses this increase above normal was hardly noticeable. In the few animals

that survived large doses, the thrombopenia lasted many days (18 in one instance) When hemorrhages into the tissues had been numerous and extensive, the platelets reached very high levels Marked variations in the size and appearance of the platelets were evident both in wet and dry stained specimens Macroplatelets appeared as early as three to four hours after the administration of the serum intraperitoneally (chart 2), when the num-

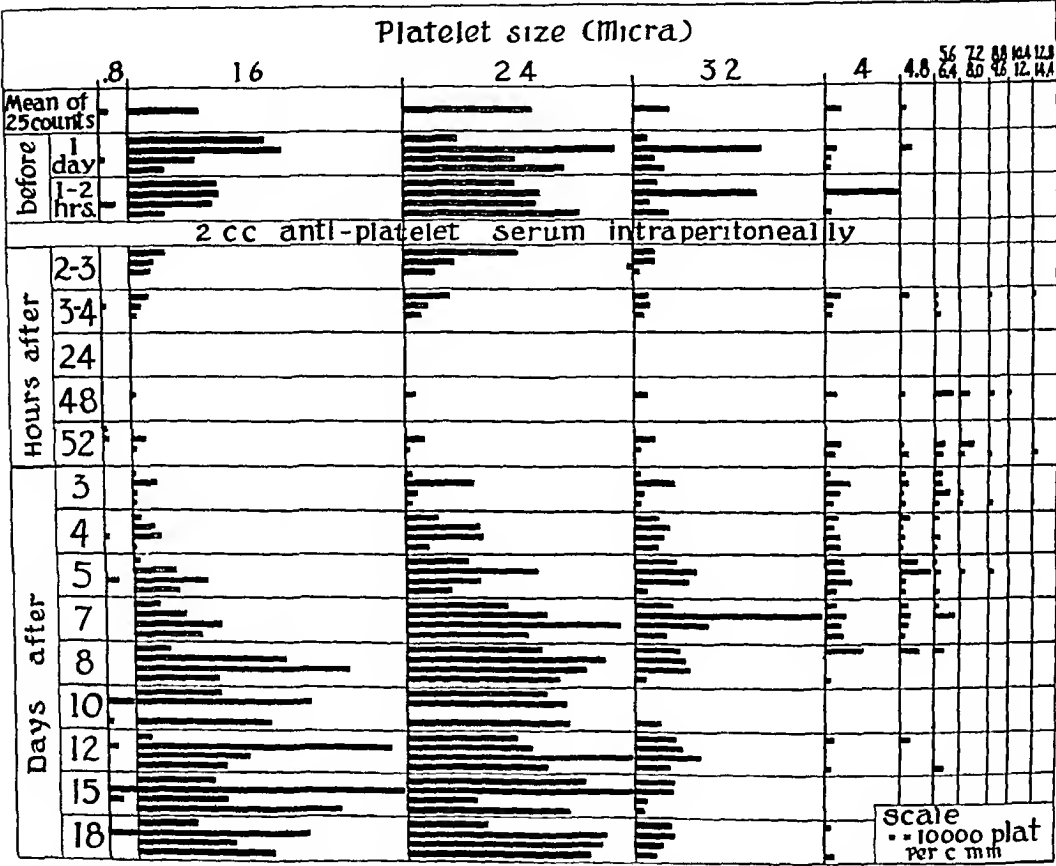


CHART 2 Variations in the size of the platelets of four dogs after the intraperitoneal injection of antiplatelet serum (one count lost on tenth day)

ber of platelets had only been decreased from one-half to two-thirds of their normal level They were not observed in the next 24 hours but reappeared as the platelet level began rising and were greatest in number from 52 to 72 hours after the injection, when the largest forms were usually seen For the next four days they decreased steadily in numbers and eventually were replaced by smaller forms At this stage great irregularity in their size was evident In contrast to normal platelets, they exhibited no hyalomere, were intensely basophilic and filled with dark, coarse granules, a few had a fibrillated cytoplasm The appearance of macroplatelets often coincided with the return of the bleeding time to normal and the beginning of the rise in the platelet level (chart 1) Of 17 dogs on which these observations were

made, 10 showed macroplatelets for the first time (during the course of the purpura) simultaneously with the return of the mean bleeding time to normal, 5, with the last long bleeding time determination, and 2, one and two days, respectively, after the bleeding time had returned to normal. Their appearance coincided with the return of retractility to the clot and a diminution in the skin petechiae reaction (chart 1). They were seldom observed in appreciable numbers after the platelets rose to higher levels.

Erythrocytes After an intraperitoneal injection of a moderate dose, the erythrocytes invariably showed a slight reduction in numbers within 24 hours (chart 1). Decreases were evident during the acute phase of purpura when hemorrhages were prevalent and the bleeding time prolonged. After the hemorrhagic period ceased, they returned slowly to normal. After repeated moderate doses similar observations were made (chart 3). Large

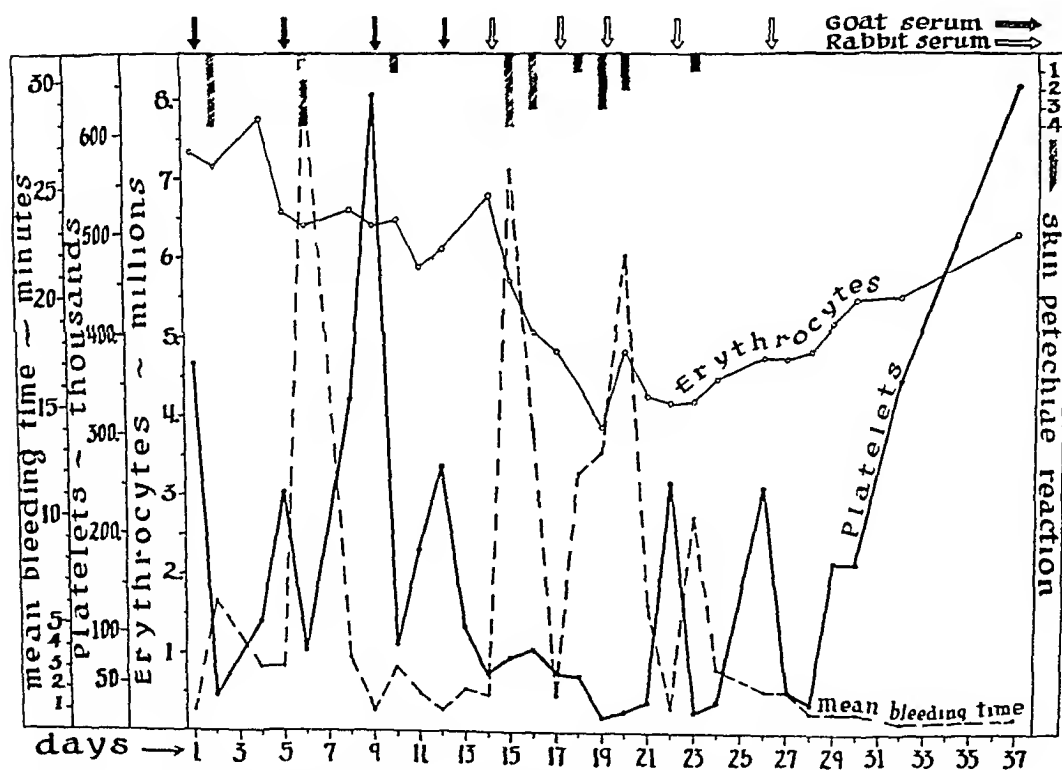


CHART 3 Effect of repeated injections of anti-dog-platelet goat serum followed by repeated injections of anti-dog-platelet rabbit serum in one dog

doses of the serum and the consequent longer phase of purpura depressed the erythrocytes in four animals to a level below one million per cu mm. Normoblasts appeared in the peripheral blood following these phases, after a particularly severe hemorrhage in one dog they made up 36 per cent of the total number of red blood cells. Hemolysis in variable degree was always observed in the blood smears during the acute stage of the attack.

Leukocytes A slight leukopenia often appeared within the first six hours after an intraperitoneal injection. It was generally followed the next day by a leukocytosis which lasted for several days (chart 1). The initial decrease in the leukocyte count took place at the expense of the lymphocytes, monocytes, and eosinophiles, even before the platelets had been reduced to their lowest levels. Twenty-four hours after those cells began a return to their former level, the monocytes usually went beyond it 52 hours after and the lymphocytes four days afterwards. The eosinophiles did not go beyond the level previous to the injection. The rise in the total leukocyte count resulted chiefly from an increase in the polymorphonuclear neutrophils. The peak of this rise coincided with the first evidence of an increase in the platelet level of the peripheral blood. As the platelets rose, the polymorphonuclear neutrophils returned gradually to their previous level, the relative proportions between the other leukocytes not showing any significant changes. An immediate and marked leukopenia, which lasted a few hours, usually followed an intravenous injection of a moderate dose, within the first 5 minutes after such an injection, leukocytes swollen to twice their usual size, enmeshed in clumps of lysed platelets, were often observed in fresh wet preparations of the peripheral blood.

MEAN BLEEDING TIME

With moderate doses intraperitoneally the mean bleeding time first showed a prolongation from three to five hours after the injection (chart 1), sometimes even before the platelets had dropped below 100,000 per cu mm, it remained prolonged for 24 to 48 hours occasionally longer, but rarely more than four days. Cuts made in the oral mucous membrane likewise yielded a prolonged bleeding time during the acute phase. Four minutes after an intravenous injection, a prolongation in the mean bleeding time could be detected. At the height of an acute phase, the ear vein of one of the animals slowly dripped blood continuously for several hours while all about the wound hung thick, stratified blood clots. In animals that survived large doses, a prolongation was maintained for several days 11 days in two instances. Repeated injections of small or moderate doses at short intervals eventually failed to prolong the bleeding time while still having a destructive effect on the platelets (chart 3). Eventually even the effect on the platelets was lost. Animals differed in the number of doses necessary to bring about this refractoriness. One animal became refractory after one moderate dose, another, after seven such doses.

Normally the bleeding time from the ear vein is greater in volume of output of blood per 15 seconds than that of the skin of the abdomen and thigh. During the acute phase of purpura, the bleeding time of many of the animals exhibited wide variations in the output of blood in a given time interval, a fairly small drop would be followed by one from one-half to five times its size, then large drops appeared in quick succession for the next two

or three minutes with a return to the drops of small size and so on, alternately. The volume output of blood in a given time interval varied remarkably in some instances. A better idea was formed of these variations by collecting the blood issuing from the ear vein at 15 second intervals and measuring it. Various rates of flow were obtained representing normal values (chart 4). During the acute stage the volume output of blood was visibly increased and irregular, whereas after recovery the opposite was observed. Toward the end of the phase of hemorrhages, and one day or more before the platelet count had shown an increase, the bleeding time from the ear vein often showed this peculiarity: after a minute or so of a profuse flow of blood there would be a sudden stop with no subsequent bleeding. When the platelet count was above normal levels the bleeding time became unusually short both in duration (chart 1) and volume of output, often a cut into the skin would yield no blood whatever. It was then that the skin was unusually tense and pale, the fine skin and conjunctival vessels being hardly visible.

Changes in the Coagulation of the Blood The destruction of platelets by antiplatelet serum injected intraperitoneally produced at first a diminution in the coagulation time of the blood, followed by a period of instability appearing between 28 and 72 hours afterwards and finally by a return to the normal duration (chart 1). After the intravenous administration of the serum the blood also became hypercoagulable during the initial period of platelet destruction (the first few minutes after the injection). That phase was soon replaced by one of prolonged coagulation with a slow return to normal as the platelets reached their former level. A slight prolongation of the clotting time of the blood in rabbits¹¹ and dogs¹² has been found after intravenous injections of antiplatelet serum, with a slow return to normal accompanying the rise in the platelets. Such was thought to be the usual sequence of events after an injection of that serum. To detect the phase of hypercoagulability, however, it is necessary to collect the blood during the actual period of platelet destruction, or, say, in the first three to four minutes when the serum is given intravenously, and within the first three to five hours when given intraperitoneally. The phase of hypercoagulability is perhaps the result of the great number of destroyed platelets in the circulation, the subsequent period of thrombopenia may partially account for the delayed coagulation.

Clot Retraction The method of judging this property of the clot depends on the setting of an arbitrary standard for irretractility⁴ since platelet-free clots are normally capable of retraction under favorable conditions, as, for example, when forces of adhesion are not dominant. With clots handled under specified conditions, spontaneous syneresis diminished along with the decrease in the number of platelets and was absent when they went below approximately 70,000 (chart 1). It disappeared within the first 10 minutes after an intravenous injection. During the period of purpura, the clots appeared soft, fractured easily, did not hold their shape when removed from

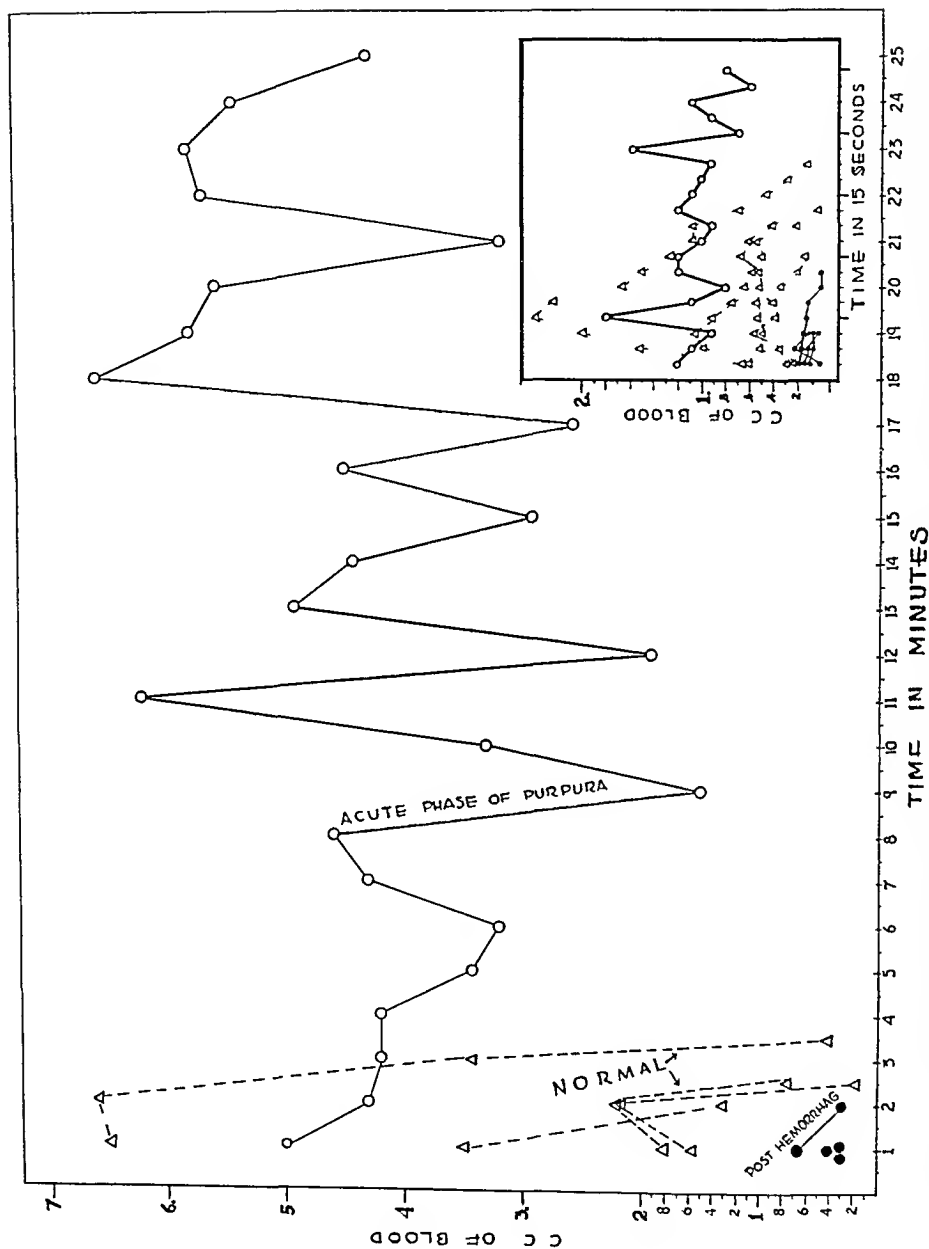


CHART 4 The volume output of blood from the ear vein in a normal dog, and during and after a phase of purpura. Inset: the first five-minute period of the curves in the main graph plotted in terms of the actual amount of blood collected at 15 second intervals

the vessel, and did not dry for 24 hours and longer. Clots became strongly retractile, however, before the platelets had shown a substantial increase from their low level (chart 1)

Correlations All correlations were apparently linear since no significant difference could be found between each coefficient and its corresponding ratio, when Blakeman's⁸ test was applied. The highest correlation was between the number of platelets and the degree of clot retraction ($+0.759 \pm 0.024$). Second to it was that between the bleeding time and the degree of clot retraction (-0.630 ± 0.04). These two correlations are not higher perhaps because of deficiencies in the method of measuring clot retractility. The moderately high correlation found between the bleeding time and the degree of the skin petechiae reaction ($+0.546 \pm 0.022$) may be traced to the influence of parallel changes in the number of platelets. That the correlation is not higher suggests that these changes alone do not account for the phenomena observed and that other factors must be searched for. The moderate degree of correlation between clot retractility and the skin petechiae reaction (-0.554 ± 0.039) may likewise be traced to changes in a common factor, the platelets, thereby influencing both phenomena simultaneously. There was an inverse correlation, moderately high, between the venous clotting time and the units of clot retraction (-0.462 ± 0.044), which may be explained in a similar manner.

The degree of correlation between the platelets and the bleeding time (-0.424 ± 0.026), and the platelets and petechiae reaction (-0.400 ± 0.027), was lower than anticipated. It was lower than the correlation between the bleeding time and petechiae reaction or between either one of these and clot retraction. This points to a closer relationship of the bleeding time and petechiae reaction with the character of the clot than with the platelet level of the blood. The diminution in the retractile power of thrombopenic clots may be related to the diminution or loss of elasticity of the skin observed during the height of an attack of purpura.

The similarity in degree between the coefficients for the platelets and bleeding time, and the platelets and the petechiae reaction suggests that whatever factors, aside from the platelets, influence the bleeding time, perhaps also play a part in the skin petechiae reaction. The relatively lower degree of these two correlation coefficients is another point favoring the existence of these other factors. There was a low correlation, not significant, between the mean bleeding time and the clotting time ($+0.113 \pm 0.056$), this helps to reinforce the impression obtained clinically that changes in the coagulation time of the blood have very little effect on the bleeding time. There was likewise a useless correlation, of no significance, between the number of platelets and the clotting time of the blood (-0.234 ± 0.069). This indicates that, although the platelet undoubtedly plays a part in the coagulation of the blood, this phenomenon is so complex that the rate of coagulation cannot be predicted from the number of circulating blood platelets alone. It also suggests that whatever disturbances in hemostasis were

the result of the destruction of platelets, changes in the coagulation of the blood did not contribute a large share in originating or perpetuating them

DISCUSSION

If macroplatelets may be considered as evidence of increased or abnormal platelet regeneration, it is clear that this may begin within from three to four hours after the platelets have been moderately reduced in numbers by the antiplatelet serum. Their subsequent disappearance and absence during the next 24 hours may be evidence that the young forms are destroyed by the circulating anti-serum or that no new forms can be regenerated because of a disabling effect of the serum on the thrombopoietic tissues. Perhaps the initial effect of the serum on these tissues is a stimulation to greater activity, followed by a depression during which no giant forms are observed. The uniform rhythm of their appearance also argues strongly against the proposed theory that "in vivo" the platelets are not destroyed by the serum¹² and that their disappearance from the peripheral blood is only temporary. If these forms bear a relationship to the mature platelet similar to that of the reticulocyte to the red blood cell, then the response of the marrow to a sudden decrease in the number of circulating platelets is approximately as rapid as the response of reticulocytes after a hemorrhage. Steele¹³ found that the reticulocyte percentage of rabbits bled out of 35 per cent of their blood, increased within a few hours after the bleeding.

The variations in the volume output of the blood from wounds during the various stages of purpura suggest changes in the normal distribution of blood among the vessels or alterations in their caliber, or in the pressure within them. A bleeding time shorter than normal appears to have been previously recorded only by Russell¹⁴ in canaries with chronic malaria.

The correlation between the number of platelets and the bleeding time was not as high as might have been expected. This is perhaps because (a) The number of circulating platelets may not give a true idea of the actual number of available functioning platelets in the blood at a given time. An increased utilization of platelets may take all the platelets being regenerated and leave no balance to swell the numbers in the circulation, this would explain the low platelet count with a normal bleeding time, if the latter were almost exclusively a function of the platelets. (b) Collateral forces of hemostasis of a vascular or extra-vascular nature may take a hand in the control of the bleeding during the thrombopenic interval. The demonstration of the presence and nature of such forces is difficult until more extended studies of the vessels are available. The return of the tonicity of the skin to normal before the platelets have reached a high level may partially account for the diminution in the bleeding time. With two exceptions, no really high correlations were found, which emphasizes the complexity of the mechanism of hemostasis and the multiplicity of factors involved in maintaining its integrity. Among these factors should be considered the permeability of the vessels, the capillary and venous pressure, the colloid osmotic pressure

and viscosity of the blood and the tension or elasticity of the tissues adjacent to the vessels. These forces are known to play a part in the movement of fluid to and from the vessels, it is natural to suspect them of influencing the escape of blood.

SUMMARY

Various cytological and physical changes in the blood of dogs with experimental thrombopenic purpura are described and an analysis made of the extent of the correlation between these changes themselves and the external manifestations of the disease.

Morphological variations in the platelets were regularly observed soon after a diminution in their level in the peripheral blood as well as preceding their return to normal after a period of thrombopenia.

The volume and rate of output of blood per unit time from a skin wound were increased and irregular during the acute phase of purpura and became markedly decreased in the first few days following recovery.

The highest correlations found were between the number of platelets and the degree of clot retraction, and between the latter and the mean bleeding time.

The correlations were of such a degree as to indicate that other factors than those under analysis will be found to play important rôles in the mechanism of normal and impaired hemostasis.

I am indebted to Drs. Thomas McCrae and H. W. Jones for their sympathetic support and to Miss Katherine Pierpoint for efficient technical assistance.

REFERENCES

- 1 WRIGHT, J. H., and KINNICUTT, R. A new method of counting the blood platelets for clinical purposes, *Jr. Am. Med. Assoc.*, 1911, *lv*, 1457-1459.
- 2 GRAM, H. C. Blood platelets in influenza, with remarks on the technic of counting, *Acta med. Scandinav.*, 1920, *liv*, 1-6.
- 3 FONIO, A. Die Bestimmung der Prognose der Blutstillung, Zentrifugiermethode, *Archiv f. klin. Chirur.*, 1928, *cliv*, 459-476.
- 4 TOCANTINS, L. M. Platelets and the spontaneous syneresis of blood clots, *Am. Jr. Physiol.*, 1934, *cx*, 278-286.
- 5 DUNN, H. L. Application of statistical methods in physiology, *Physiol. Rev.*, 1929, *ix*, 275-398.
- 6 PEARL, R. Introduction to medical biometry and statistics, 1923, W. B. Saunders and Co., Philadelphia.
- 7 DAY, E. E. Statistical analysis, 1925, Macmillan and Co., New York.
- 8 BLAKEMAN, J. On tests for linearity and regression in frequency distributions, *Biometrika*, 1905, *iv*, 332-350.
- 9 TOCANTINS, L. M. Experimental thrombopenic purpura in dogs, *Arch. Pathol.* (In press).
- 10 AYNAUD, M. Le globulin des mammifères, *These de Paris*, 1909.
- 11 ROSKAM, J. Purpuras hemorrhagiques et thrombopenie, *Sang.*, 1934, *viii*, 129-169.
- 12 SACERDOTTI, C. Le piastrine dei mammiferi e il siero antiplastrinico, *Arch. per le sc. med.*, 1908, *xxvii*, 338-404.
- 13 STEELE, B. F. Effects of blood loss and blood destruction upon the erythroid cells in bone marrow of rabbits, *Jr. Exper. Med.*, 1933, *lvii*, 881-896.
- 14 RUSSELL, P. F. Avian malaria studies. VIII. Bleeding time in canaries, normal and in malaria, *Philippine Jr. Sci.*, 1932, *xlix*, 627-647.

A COMPARISON OF THE RATE OF ABSORPTION FROM NORMAL AND BURNED TISSUES [†]

By EDWARD C MASON, M D , F A C P , PEARL PAXTON, M S , and H A SHOEMAKER, Ph D , *Oklahoma City, Oklahoma*

IN 1925, Mason, Davidson et al published a series of papers,^{1, 2, 3} recording the observations made on animals which died in 15 to 18 hours as a result of a small piece of liver tissue left free within the abdomen. While doing this work, we conceived the idea that death following burns was probably due to the same factors which caused the death of these animals. Davidson,⁴ at the suggestion of Mason, introduced the tannic acid treatment of burns on the assumption that tannic acid would precipitate the dead and dying tissues and thereby prevent the absorption of toxic materials. The splendid results obtained by Davidson, and subsequent workers, apparently justified our theory.

The theory of toxic absorption accompanying burns has been held by numerous authors, and a variety of substances has been claimed responsible for the cause of death following burns. A very comprehensive list of such substances may be found in the paper of Fender,⁵ on the subject of "Lymphatic Pathology in Relation to 'Toxins' of Burns". More recently, Underhill^{6, 7, 8, 9} expressed the idea that no absorption occurred from burned areas, and in support of this contention he presented data which showed delayed absorption of such substances as strychnine and phenolsulphonephthalein from burned areas. From his observations he concluded that within a period of less than two hours following a burn there is a marked increase in permeability. "The increased permeability of capillaries appears to be in one direction only, namely from the blood to the tissue fluids. From the tissue fluid to the blood there is an apparent decreased permeability."⁷ As a result of his studies, Underhill stressed the replacement of body fluids, lost from the burned area, as the principal therapeutic measure. He considered that the local treatment of burns was of secondary importance. We have continued the study in order to determine if substances other than strychnine and phenolsulphonephthalein are absorbed from burned areas. We have selected potassium iodide, a readily diffusible substance of relatively low molecular weight, and have studied the rate of excretion following subcutaneous injections in normal and burned animals.

EXPERIMENTAL

Normal rabbits were used to determine the rate of excretion of potassium iodide injected beneath the skin of the abdomen, the amount of potas-

[†] Presented before the American Physiological Society, Detroit, Michigan, April 13, 1935

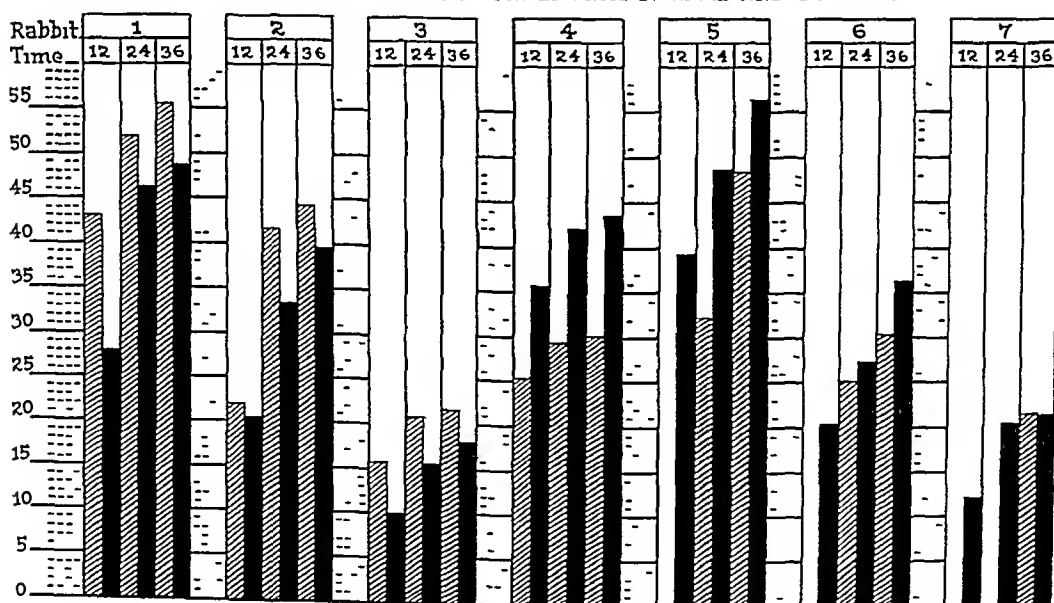
From the School of Medicine, University of Oklahoma

sium iodide being 5 c c of a 2.29 per cent (approximately isotonic) solution per kilogram of body weight. The per cent of potassium iodide excreted by such normal rabbits varied greatly, the greatest total excretion for 36 hours being 55.4 per cent of the total potassium iodide injected, while the lowest was 21.7 per cent. Repeating the determinations, we found that animals which excreted a high percentage on the first test also excreted approximately the same amount on the second test and, likewise, those excreting a low percentage on the first test also excreted a low percentage on the second. The urine was collected by catheterization each 12, 24 and 36 hours following the injection. The amount of potassium iodide excreted was determined by a method developed by one of us (H. A. S.¹⁰) which is an adaptation from a variety of existing methods. Briefly, the method includes the destruction of the organic material by oxidation and the conversion of the iodide to iodate by bromine water in a slightly acid solution. Potassium iodide is added, and the liberated iodine is titrated, using sodium thiosulphate with starch as the indicator.

While the animals were completely anesthetized, a burned area was produced on the abdominal surface, and six hours following the burn, potassium iodide was injected subcutaneously in the burned area, the amount of potassium iodide used being the same per kilogram of body weight as was injected into the normal rabbits.

The data obtained from the normal and burned rabbits appear in the following table:

THE RATE OF EXCRETION OF IODIDES ABSORBED FROM NORMAL AND BURNED AREAS



The cross-hatched bar represents iodide excretion by the normal animals.
The solid black bar represents iodide excretion by the burned animals.

The values are expressed as the total per cent of potassium iodide recovered at the end of 12, 24 and 36 hours. It will be observed that the excretion is essentially the same in both the normal and burned animals. Three rabbits excreted slightly more in the normal state and three excreted slightly more in the burned state. While one animal's output was practically the same before and following the burn, this rabbit No. 7, developed a respiratory infection during our study and died shortly after the completion of the experiment. No urine was obtained from rabbit No. 6 by catheterization at the end of the first 12 hours, and none was obtained from normal rabbit No. 7 for the 12 and 24 hour periods, however, by washing the cage and collecting the total output, we obtained results quite comparable to the other rabbits.

DISCUSSION

The experience during the late World War demonstrated the fact that the absorption of extracts of freshly crushed tissue and extracts of autolyzed tissue caused toxic symptoms. The generally accepted treatment became that of debridement, and the results verified the contention that a wound freed of dead and dying tissue gave the patient a better chance for recovery. This theory was also strongly supported by the studies of Cannon¹¹ on wound shock.

More recently this old conception has been attacked,^{12, 13} and evidence has been presented to support the theory that with the presence of injured tissue injured either mechanically or by burning, there occurs an outpouring of body fluid into the injured area, and such fluids represent blood serum or blood plasma. It is further claimed that the resulting blood concentration will account for all the symptoms and pathological changes which occur in "secondary shock."

In support of the older idea of "wound shock," Mason and Nau¹⁴ have recently presented evidence that the absorption of products of autolysis of sterile liver does produce definite pathological changes within the host. Also, the marked decrease in mortality,¹⁵ from 28 to 15 per cent, resulting in the use of tannic acid in the treatment of burns suggests that the toxic material is precipitated by the tannic acid and its absorption prevented. Quite recently Blalock has agreed that the absorption of extracts of injured tissue (burned tissue) may be the cause of shock. The following quotation is taken from his discussion¹⁶: "First, I would like to state that I believe some instances of shock are due to the absorption of toxic products. The action of toxic material is probably the main factor in producing death in the patient who has intestinal obstruction with strangulation of the blood supply. I believe that deaths which occur from three to ten days following severe burns are due in large part to the absorption of protein decomposition products."

CONCLUSIONS

1 A readily diffusible substance of low molecular weight, such as potassium iodide, is absorbed from burned areas

2 Death occurring several days following severe burns is due mainly to the absorption of protein decomposition products

BIBLIOGRAPHY

- 1 MASON, E C, and others Study of tissue autolysis in vivo, blood changes physical and chemical, Jr Lab and Clin Med, 1925, x, 622-630
- 2 MASON, E C, DAVIDSON, E C, and RASTELLO, P B Study of tissue autolysis in vivo, pharmacological study of toxic material, Jr Lab and Clin Med, 1925, x, 906-913
- 3 MASON, E C, DAVIDSON, E C, and MATTHEW, C W Study of tissue autolysis in vivo, observations using spleen, Jr Lab and Clin Med, 1925, x, 997-999
- 4 DAVIDSON, E C Tannic acid in treatment of burns, Surg, Gynec and Obst, 1925, xli, 202-221
- 5 FENDER, F A Lymphatic pathology in relation to "toxins" of burns, Surg, Gynec and Obst, 1933, lvi, 612-620
- 6 UNDERHILL, F P Changes in blood concentration with special reference to treatment of extensive superficial burns, Ann Surg, 1927, lxxvi, 840-849
- 7 UNDERHILL, F P Significance of anhydremia in extensive superficial burns, Jr Am Med Assoc, 1930, xc, 852-857
- 8 UNDERHILL, F P, KAPSINOW, R, and FISK, M E Studies on mechanism of water exchange in the animal organism, Am Jr Physiol, 1930, xc, 302-314
- 9 UNDERHILL, F P, and KAPSINOW, R Alleged toxin of burns, Jr Lab and Clin Med, 1931, xvi, 823-830
- 10 SHOEMAKER, H A, and UNDERHILL, F P Distribution of chlorides and iodides in skin and muscles of rabbit after administration of potassium iodide, Jr Pharm and Exper Therap, 1932, xlv, 23-42
- 11 CANNON, W B Traumatic shock, 1923, D Appleton and Co, N Y, p 301
- 12 PARSONS, E, and PHEMISTER, D B Hemorrhage and "shock" in traumatized limbs, experimental study, Surg, Gynec and Obst, 1930, li, 196-207
- 13 BLALOCK, A Experimental shock, importance of local loss of fluid in the production of low blood pressure after burns, Arch Surg, 1931, xlii, 610-616
- 14 MASON, E C, and NAU, C A Cause of death due to liver autolysis, Surg, Gynec and Obst, 1935, lxv, 769-774
- 15 BEEKMAN, F Tannic acid treatment of burns, Arch Surg, 1929, xlviii, 803-806
- 16 BLALOCK, A (Discussion) Adrenal extract in controlling shock, Ann Surg, 1934, c, 747

STUDIES IN MULTIPLE SCLEROSIS

VIII ETIOLOGIC FACTORS IN MULTIPLE SCLEROSIS *

By TRACY J. PUTNAM, M.D., *Boston, Massachusetts*

THE EXPERIMENTAL PRODUCTION OF LESIONS SIMULATING MULTIPLE SCLEROSIS

IN previous communications, it has been pointed out that lesions closely resembling typical plaques of multiple sclerosis may be produced in animals in either of two ways—by the subcutaneous injection of minute doses of tetanus toxin¹ and by experimental obstruction of cerebral venules². In each case sclerotic lesions could be demonstrated only after an interval of several months from the original injury. The earlier lesions closely resembled those of “post-infectious encephalomyelitis,” a disease occasionally seen following measles³ and vaccinia⁴ and often without obvious antecedent. Areas of demyelination, with relative persistence of axis cylinders, accompanied by infiltration in the early stages and gliosis later, have also been described as a result of carbon monoxide poisoning with venous thrombosis,⁵ and chronic cyanide poisoning.⁶

By themselves, these experimental results prove little in regard to the human disease of multiple sclerosis. They do suggest, however, that

1 “Post-infectious encephalomyelitis” and multiple sclerosis may represent the same pathologic process at different stages with variations in intensity.

2 Local anoxemia, or more specifically local venous obstruction, should receive consideration as the immediate cause of the primary demyelination.

3 The process may be precipitated in some way by an organic toxin, and probably by any one of many.

None of these propositions is entirely new, but apparently no attempt has been made to interrelate them. Indeed, they have been considered almost mutually exclusive. Thus multiple sclerosis has been looked upon as a toxic disease, and therefore not circulatory, or as an infectious disease and therefore not toxic. Before attempting to harmonize these points of view, let us see what may be said for each of them separately.

“ENCEPHALOMYELITIS” AND MULTIPLE SCLEROSIS AS MANIFESTATIONS OF THE SAME PATHOLOGIC PROCESS

The essential similarity between “encephalomyelitis” (especially the post-measles and post-vaccinal forms) and multiple sclerosis has frequently

* Received for publication October 3, 1935. (Presented before the Section of Nervous and Mental Diseases of the American Medical Association, Atlantic City, June 12, 1935.)

From the Neurological Unit, Boston City Hospital and the Department of Neurology, Harvard Medical School, Boston, Massachusetts.

The expenses of this investigation were defrayed in part by the Multiple Sclerosis Fund of Harvard University.

been affirmed,⁷ and almost as frequently denied⁸ The points of similarity between the two diseases which are usually pointed out are the patchy distribution of the lesions, which surround venules of the white matter, and the predominant involvement of myelin, axis cylinders often remaining relatively intact On the other side of the question, it has been asserted that the lesions of the acute disease are more diffuse than those of multiple sclerosis, and this is doubtless true in some instances In these cases the picture as a whole is much more similar to that of diffuse sclerosis or Schilder's disease This condition, however, is probably to be considered a variant of multiple sclerosis⁹ Further, it has been objected that there is much more extensive loss of axis cylinders in the lesions of "disseminated encephalomyelitis" than in typical sclerotic plaques This is probably true, but it must be remembered that the patient has died at the height of a severe acute process in most cases of the former disease coming to autopsy, while a milder process, such as multiple sclerosis, might be expected to allow the survival of axis cylinders in greater numbers Even in multiple sclerosis, extensive loss of axis cylinders is common, as all modern investigators have reported In a series of 35 separate plaques from 11 cases of multiple sclerosis studied with this question in mind, almost complete destruction of axis cylinders was found in eighteen¹⁰ A case reported by Walthard¹¹ is often cited as direct evidence that post-measles "encephalitis" is not the equivalent of multiple sclerosis The patient died three months after a typical onset, and at autopsy a considerable loss of axis cylinders was found in most of the lesions Perhaps more relevant, however, may be the cases of Cramer¹² and of Schlesinger,¹³ in both of which the patients survived an unmistakable post-infectious "encephalitis" for many months and in both of which typical sclerotic plaques (figure 1) containing relatively intact axones were found post mortem Walthard's case may then be considered a transitional form of which a number have been reported^{8, 14 15}

Gliosis, which is a striking feature of multiple sclerosis, would scarcely be expected in an acute process It is, however, not as specific for multiple sclerosis as has sometimes been supposed Lesions with loss of myelin but with little or no gliosis occur side by side with typical sclerotic plaques, and on the other hand, areas of secondary degeneration in other pathologic conditions of comparable age and intensity with those of multiple sclerosis develop quite as dense a glial scar (Figures 2 and 3) It is probably a general rule that once myelin has been broken down, it cannot regenerate in the adult central nervous system,¹⁶ and that myelin loss is repaired by a glial fibrosis which grows denser and less cellular with the passage of years An exception to the rule is seen in such conditions as the degeneration accompanying primary anemia, in which gliosis appears to be inhibited by some nutritive lack

Additional points of similarity between "encephalomyelitis" and multiple sclerosis, which have apparently escaped notice, are the vascular ob-



FIG 1 Typical sclerotic plaques in the pons, from the brain of a boy of 7, who died 22 months from the onset of a clinically typical post-measles "encephalomyelitis," after a course marked by remissions and exacerbations (After Schlesinger¹³)

structions and engorgement and the perivascular hemorrhages seen in both, as will be described below

It is assumed by most writers on the subject, often without any display of evidence, that an "encephalomyelitis" in which an infiltration with hematogenous cells occurs must be due to a filterable virus if it occurs in the course of a virus disease. Infiltration with lymphocytes and leukocytes is, however, common in the vicinity of softenings and tumors¹⁷. Further, Rivers¹⁸ has pointed out that all known virus diseases lead primarily to either a necrosis or a proliferation of parenchymal cells, or both, while in "encephalomyelitis" of the type in question the chief damage is to cell appendages, and in particular to the myelin which is probably to be considered as intercellular substance¹⁹.

VASCULAR LESIONS AND DEMYELINATION

In addition to the experimental data already presented, there is evidence from the pathology of other diseases that disturbance of circulation may lead to loss of myelin and to gliosis. Thus the ordinary forms of arterio-

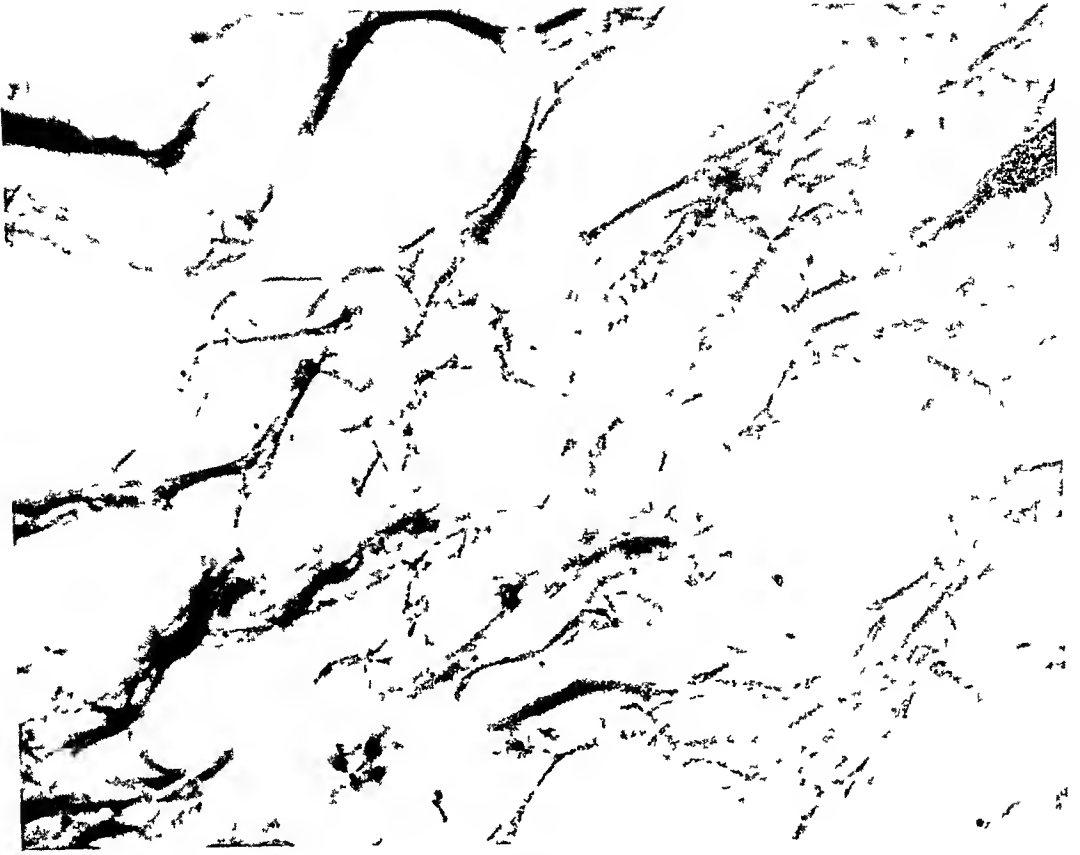
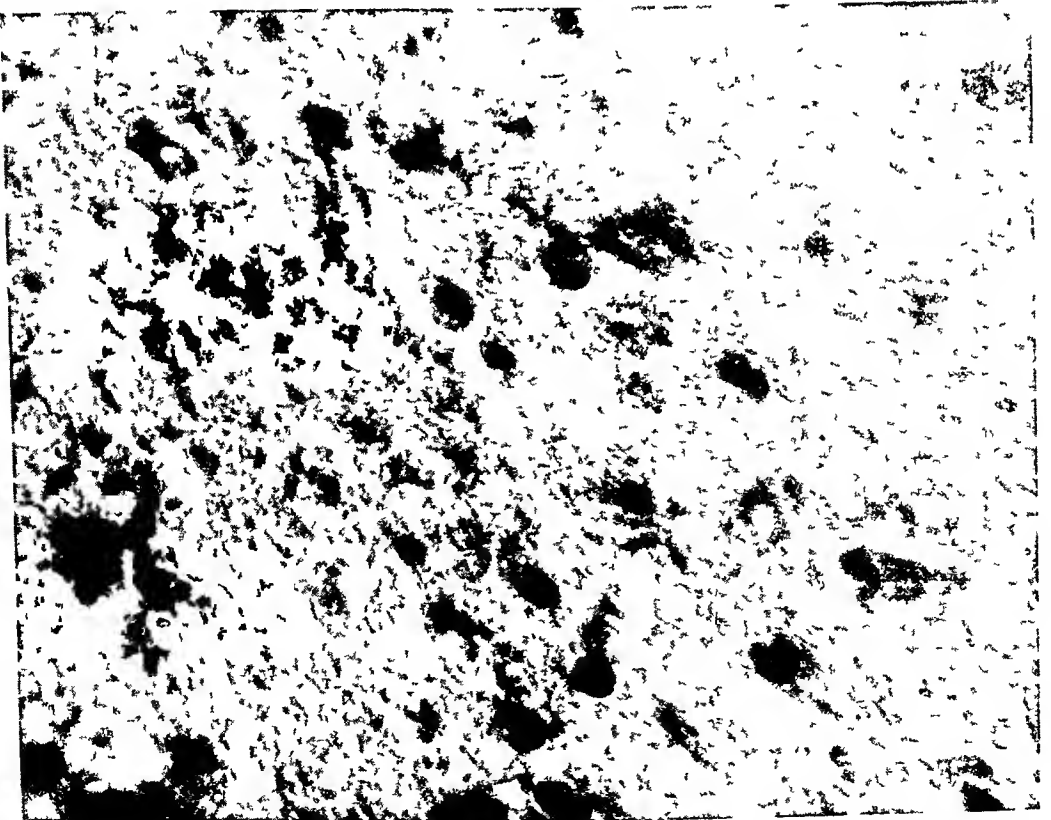


FIG 2



FIGS 2 and 3 Loose filmy gliosis (figure 2) from a plaque from a long-standing case of multiple sclerosis, for comparison with the dense gliosis in a degenerated pyramid (figure 3) secondary to a capsular apoplexy 10 years previous. Note also the absence of axis cylinders in the sclerotic plaque. Masson stain, oil immersion lens.

sclerosis may produce small lesions in the nervous system in which the myelin suffers far more than the axis cylinders. In human as well as in experimental carbon monoxide poisoning, areas of demyelination may be situated in relation to thrombosed veins,⁵ and in one well studied case, exposure to carbon monoxide apparently precipitated a fatal exacerbation of multiple sclerosis.²⁰ In the condition known as chronic subcortical encephalopathy, plaques closely resembling those of multiple sclerosis occur obviously as a result of vascular obstruction.²¹

Alterations in the blood vessels have long been recognized in multiple sclerosis, and formerly a good deal of emphasis was laid upon them as possibly of importance in the etiology of the disease, for example, by Williamson,²² Ribbert,²³ and Borst.²⁴ It was usually assumed that the vascular abnormality permitted the escape of a toxin or "toxic lymph" into the substance of the brain. More recent writers, such as Hassin,²⁵ have dismissed the vascular changes as secondary to the parenchymal degeneration. The perivascular infiltration may well be accepted as the cause of adventitial proliferation, but it seems open to question whether the obstructions, dilations, and perivascular hemorrhages which have been described could be explained on a similar basis.

In "post-infectious encephalomyelitis" vascular engorgement has been reported by most observers, thromboses by several, and perivascular hemorrhages by some. The presence of thrombi in post-measles "encephalitis" has received especial attention from Kreider²⁶ in Feriari's laboratory.

It seemed worth while, therefore, to make a special review of the subject. This proved not as easy as had been anticipated. Aside from the difficulties of collecting material,^{*} it was found that the ordinary routine stains and the usual neuropathologic methods were entirely inadequate for a study of thrombi and finer vascular changes. Finally, Masson's stain on paraffin material was tried, and appeared satisfactory. The results of the investigation will be published in detail elsewhere, and are merely summarized here.

In a case of post-vaccinal "encephalitis" and in another histologically similar case, but without known etiology, the vascular changes may be summarized as extreme engorgement, phagocytosis of brown pigment with and without perivascular hemorrhage and intravascular clot formation. In numerous vessels, large and small, there were masses of platelets, a heavy deposit of fibrin adherent to the walls and endothelial proliferation (figure 4).

In every one of 14 cases of multiple sclerosis in which material was available for adequate study, marked vascular changes were observed. The adventitial proliferation, doubtless a result of perivascular infiltration, has already been referred to. In addition, an engorgement, tortuosity and proliferation of veins in the vicinity of plaques were striking (figure 5).

^{*}I am greatly obliged to my friends, Dr. George Hassin of Chicago, Dr. K. Loewenburg of Ann Arbor, Dr. Cyril Courville of Los Angeles, Dr. William Shaper of Pittsburgh, Dr. John Dwyer of Springfield, Mass., and Drs. S. B. Wolbach, T. Leary, F. Parker, C. S. Kubik and I. B. Akerson of this city for their kindness in supplying pathologic material.

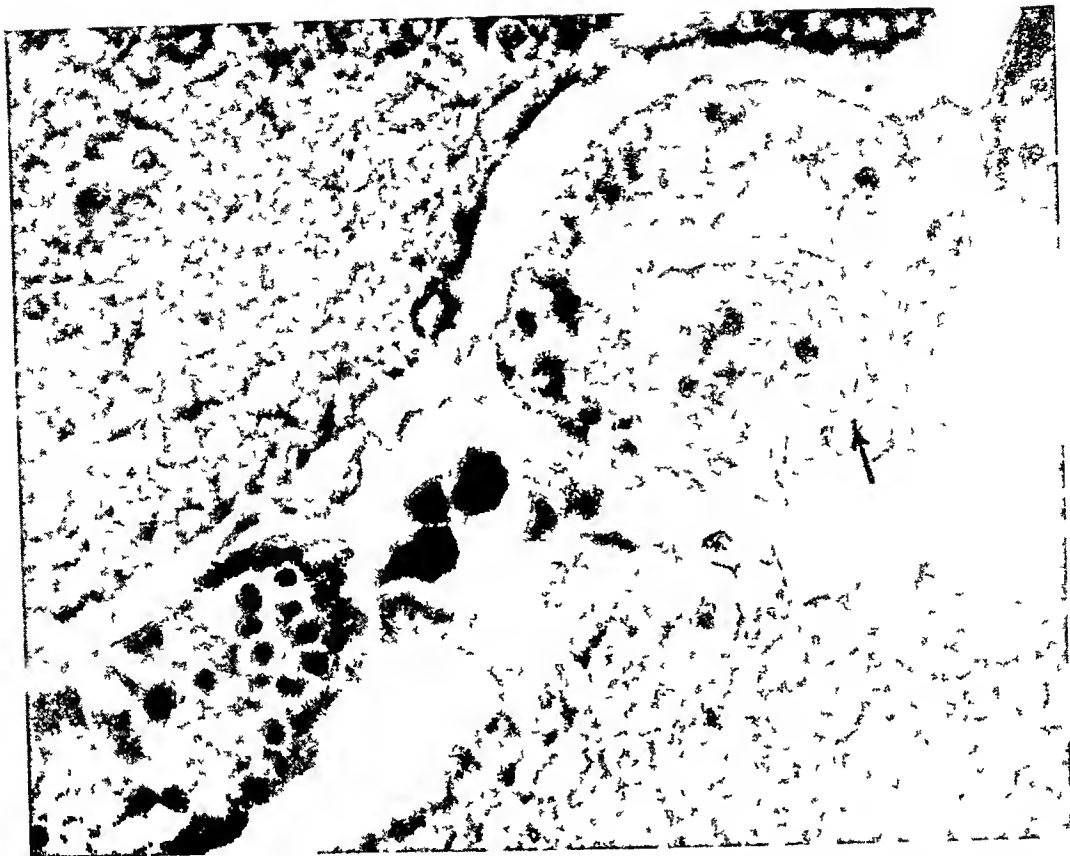


FIG 4 Post-vaccinal "encephalitis" Engorged vessel, containing a mass of fibrin adherent to the walls and clumps of leukocytes Cells are growing along a fibrin strand (arrow) Masson stain, oil immersion lens

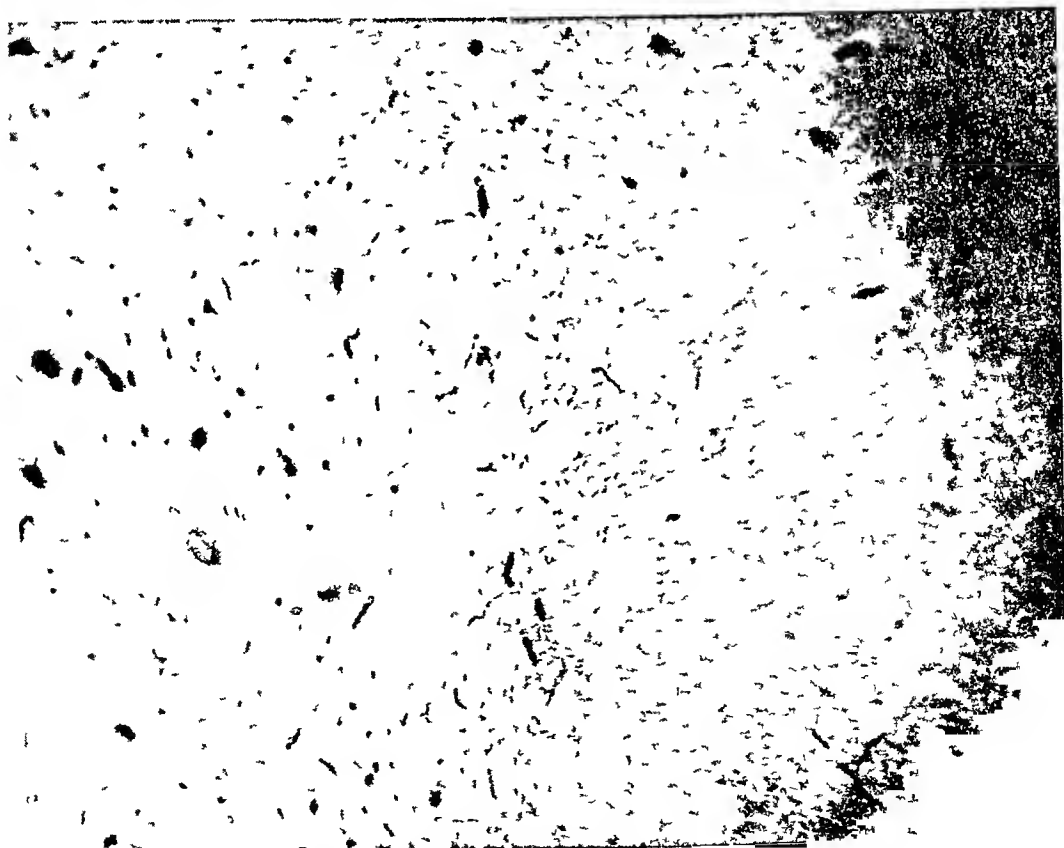


FIG 5 Multiple sclerosis Congestion and proliferation of vessels in a plaque (on left of photograph) in the cerebral white matter Masson stain, low power

Brown pigment was seen in endothelial and adventitial cells. Clots of fibrin and leukocytes occurred in vessels of various sizes, but they were less numerous and intense than in the cases of "encephalomyelitis." In some of them, invasion by endothelial cells could be demonstrated (figure 6). Complete occlusion of vessels by fibrous tissue was encountered with considerable frequency.

Can these changes be secondary to the parenchymal degeneration? A similar study was made of the vicinity of old softenings, which had produced massive secondary degenerations accompanied by dense gliosis. The vessels

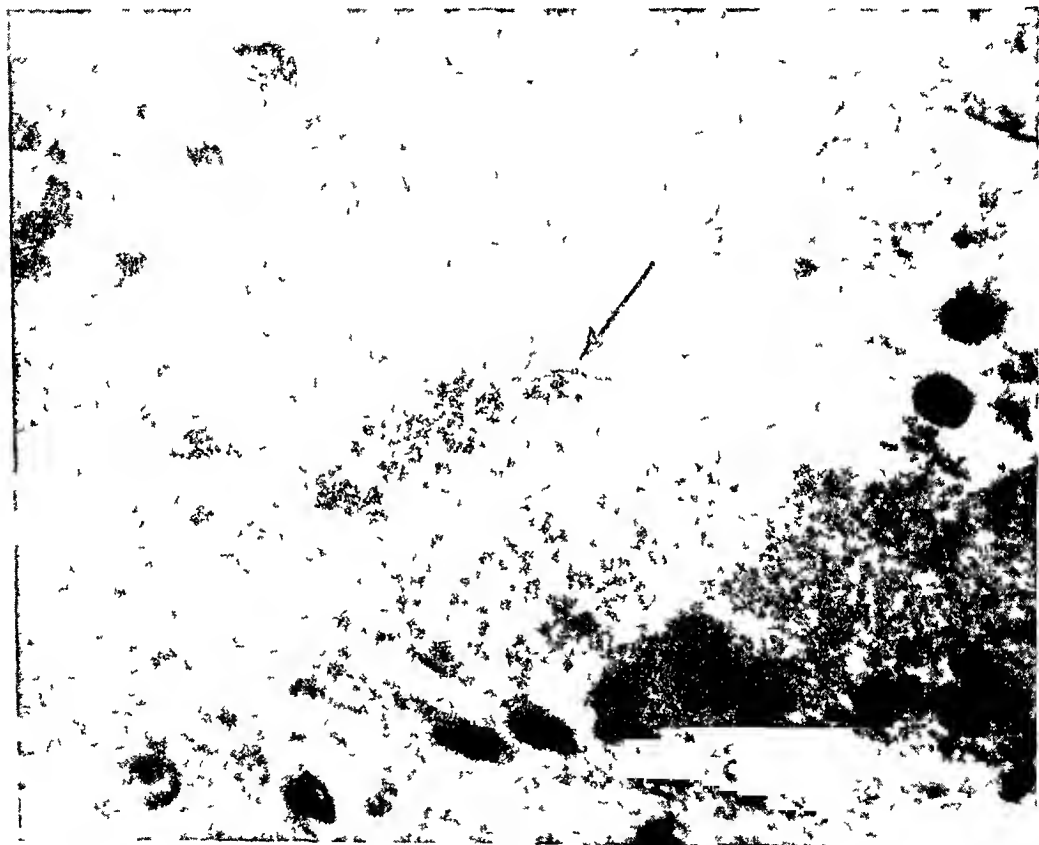


FIG 6 Multiple sclerosis. Platelet clot adherent to wall of vessel, with fibroblast (arrow) growing over the surface. Masson stain, oil immersion lens.

in such areas were approximately normal in size and number, not engorged, their walls contained no pigment, and their lumens contained no clots. There was often a thickening of the adventitia, which occasionally still held a few phagocytic cells.

Since, therefore, the vascular obstructions and dilatations seen in multiple sclerosis and "encephalomyelitis" are not regularly encountered in other types of degeneration, and since demyelination may be produced experimentally by venous obstructions, it seems reasonable to conclude that the

thromboses are primary to the changes in the nervous tissues, and not secondary. The histologic details will be discussed more fully in a paper now in preparation.

THE PART PLAYED BY TOXINS AND OTHER EXOGENOUS FACTORS

It has often been pointed out that the exacerbations of multiple sclerosis are apt to follow infections of various sorts. Pregnancy, trauma, chilling, the injection of foreign protein, and severe emotional strains are also mentioned as precipitating attacks. Von Hoesslin,²⁷ who has recently reviewed the subject, finds that one or the other of the factors mentioned appeared to be associated with the onset or progression of the disease in a large proportion of the cases which he studied. He concludes that there is probably also a predisposition to multiple sclerosis which is perhaps inherited.

If the lesions of multiple sclerosis are the result of thrombosis, it appears natural to seek the predisposing factor in the coagulating mechanism of the blood. Brickner²⁸ has described an abnormal lipolytic activity in the serum of patients suffering from multiple sclerosis, and McKenna²⁹ has pointed out that a leukocytosis is frequently found. It is not obvious, however, just how such abnormalities have a bearing on the presumed occurrence of thromboses.

The matter appears clearer since Solomon and Simon³⁰ demonstrated a functional abnormality in the clotting time in a series of patients with multiple sclerosis. Injection of adrenalin or of typhoid vaccine caused a more marked and more prolonged decrease in clotting time (that is, *increase* in coagulability) than in normal controls or patients with other neurologic diseases.

The mechanism of this increased lability of blood coagulation is still under investigation. It has been found that the blood fibrinogen is high in the majority of cases of multiple sclerosis examined. The blood calcium is within normal limits. No constant abnormality has been demonstrated in the platelet count, but in some instances there appears to be an abnormality in the behavior of the platelets. It is possible that some of the tests may be of diagnostic value.

The results of these investigations may be taken, then, to support the suggestion that some fundamental disorder of the blood leads it to clot in the cerebral venules of the central nervous system as a result of stimuli, infections, pregnancy or emotional upsets which normally would lead only to a mild increase in coagulability.

THERAPEUTIC IMPLICATIONS

No attempt has been made as yet to formulate a definite therapeutic program on the basis of the theory which has been outlined, but it is not difficult to visualize various methods which might be tried. It might be possible, for example, to lower the level of fibrinogen by diet, or to cause

a decrease in the number of platelets, or to administer a suitable anti-coagulant drug. It seems wiser, however, first to define the fundamental abnormality more clearly, if only because of the extraordinary difficulty of reaching a true estimate of the results of treatment simply from symptomatic and neurologic changes.

Obviously, the presumed exciting factors should be avoided if possible. Infections, accidents, and emotional upsets are not easily circumvented, but female patients should be advised not to become pregnant.

Certain negative conclusions are evident. Little is to be hoped for from antiseptic treatment. Heat treatment and cervical sympathectomy can have scarcely more than temporary value, if any. Treatment by injection of foreign protein is certainly to be avoided.

SUMMARY

1 The histologic features of the lesions of multiple sclerosis have been produced experimentally in animals in two ways: by the injection of minute doses of tetanus toxin, and by obstruction of cerebral venules.

2 Thrombi and obstructed vessels have been observed in the lesions of multiple sclerosis, and in those of "post-infectious encephalomyelitis," apparently an acute form of the same pathologic process.

3 It has been recognized, although rather vaguely, that there may be an association between the exacerbations of multiple sclerosis and infections, pregnancy and accidents.

4 Recent clinical investigations have shown that, although the clotting time is usually within normal limits in cases of multiple sclerosis, the coagulability of the blood is greatly increased by the administration of adrenalin or of typhoid vaccine, as compared with controls.

5 Therefore, there is probably a fundamental abnormality in the blood in multiple sclerosis, which interacts with endogenous or exogenous factors to cause thrombi in the cerebral venules.

REFERENCES

- 1 PUTNAM, T. J., MCKENNA, J. B., and EVANS, J. Experimental multiple sclerosis in dogs from injection of tetanus toxin, *Jr f Psychol u Neurol*, 1932, iv, 460-467.
- 2 PUTNAM, T. J. "Encephalitis" and sclerotic plaques from experimental venular obstruction, *Arch Neurol and Psychiat* (In press).
- 3 FERRARO, A., and SCHEFFER, J. H. Encephalitis and encephalomyelitis in measles: a pathologic report of six cases, *Arch Neurol and Psychiat*, 1931, xxv, 748-782.
- 4 HASSIN, G. B., and GEIGER, J. P. Postvaccinal (cowpox) encephalitis, *Arch Neurol and Psychiat*, 1930, xiii, 481-493.
- 5 MEYER, H. Experimentelle Erfahrungen über die Kohlenoxydvergiftung des Zentralnervensystems, *Ztschr f d ges Neurol u Psychiat*, 1928, cxii, 187-212.
- 6 FERRARO, A. Experimental toxic encephalomyelopathy, *Psychiat Quart*, 1933, vii, 267-283.
- 7 PETTE, H. Infektion und Nervensystem, *Deutsch Ztschr f Nervenhe*, 1929, cx, 221-289.
- 8 HASSIN, G. B., and BASSOE, P. Multiple degenerative softening versus multiple sclerosis, *Arch Neurol and Psychiat*, 1922, vii, 613-628.

- 9 WERTHAM, F Small foci of demyelination in the cortex and spinal cord in diffuse sclerosis—their similarity to those of disseminated sclerosis and dementia paralytica, *Arch Neurol and Psychiat*, 1932, *xxii*, 1380-1401
- 10 PUTNAM, T J Studies in multiple sclerosis VII Similarities between some forms of "encephalomyelitis" and multiple sclerosis, *Arch Neurol and Psychiat* (In press)
- 11 WALTHARD, K M Spätstadium einer "Encephalitis" nach Masern, *Ztschr f d ges Neurol u Psychiat*, 1930, *cxxiv*, 176-193
- 12 CRAMER A Beginnende multiple Sklerose und akute Myelitis, *Arch f Psychiat*, 1888, *xx*, 667-683
- 13 SCHLESINGER, H Zur Frage der akuten multiplen Sklerose und der Encephalomyelitis disseminata im Kindesalter, *Arb a d neurol Inst a d Wien Univ*, 1909, *xxii*, 410-434
- 14 CFSTAN, RISER and PLANQUEFS De la neuromyelite optique, *Rev Neurol*, 1934, *xl*, 741-762
- 15 WOHNWILL, F Zwei seltene Komplikationen bei multipler Sklerose, *Jr f Psychol u Neurol*, 1928, *xxxvii*, 408
- 16 PUTNAM, T J, MCKENNA, J B, and MORRISON, L R Studies in multiple sclerosis I The histogenesis of experimental sclerotic plaques and their relation to multiple sclerosis, *Jr Am Med Assoc*, 1931, *xcvii*, 1591-1595
- 17 CONF, W, and BARRERA, E E The brain and the spinal fluid in acute aseptic cerebral embolism, *Arch Neurol and Psychiat*, 1931, *xxv*, 523-547
- 18 RIVERS, T Filterable viruses (edited by RIVERS), 1928, Williams and Wilkins, Baltimore (See especially Chapter I by Rivers and Chapter IV by Cowdry)
- 19 DE RENZI, G S The structure of cells in tissues as revealed by microdissection II The physical properties of the living axis cylinder in the myelinated nerve fiber of the frog, *Jr Comp Neurol*, 1929, *xlvi*, 405-425
- 20 HILPERT, P Kohlenoxydvergiftung und multiple Sklerose, *Arch f Psychiat*, 1929, *lxxxix*, 117-130
- 21 GLOBUS, J H, and STRAUSS, I Progressive degenerative subcortical encephalopathy, *Arch Neurol and Psychiat*, 1928, *xx*, 1190-1228
- 22 WILLIAMSON, J B The early pathological changes in disseminated sclerosis, *Manchester Med Chron*, 1894, *ix*, 373
- 23 RIBBERT, H Über multiple Sklerose des Gehirns und Rückenmarks, *Arch f path Anat u Physiol*, 1882, *xc*, 243
- 24 BORST Die multiple Sklerose des Zentralnervensystems, *Ergebn d allg Pathol u path Anat*, 1903-1904, *ix*, 67
- 25 HASSIN, G B Studies in the pathogenesis of multiple sclerosis, *Arch Neurol and Psychiat*, 1922, *vii*, 589-607
- 26 KRUIDER, P G Measles encephalomyelopathy with venous thrombosis (To appear)
- 27 VON HOESSLIN, R Über multiple Sklerose Exogene Aetiologie, Pathogenese und Verlauf, 1934, Lehmann, München
- 28 BRICKNER, R M Studies on the pathogenesis of multiple sclerosis, *Arch Neurol and Psychiat*, 1930, *xxiii*, 715-726
- 29 MCKENNA, J B The incidence of fever and leukocytosis in multiple sclerosis, *Arch Neurol and Psychiat*, 1930, *xxiv*, 542-549
- 30 SOLOMON, P, and SIMON, B The blood coagulation in multiple sclerosis (abstract only), *Jr Nerv and Ment Dis*, 1935, *lxxxi*, 69

CORRELATIONS OF THE ENDOCRINE SYSTEM ¹

By DAVID LANDBOROUGH THOMSON, PH D, *Montreal, Canada*

UNTIL recent years, all discussions of the interrelations of the different endocrine glands were in effect discussions of a single simple diagram which was introduced by Eppinger, Falta and Rudinger ¹ as long ago as 1908, and which is still to be found in certain textbooks of physiology and of medicine at the present day. The diagram took the form of a triangle, whose apices represented the pancreas, the thyroid, and the adrenal medullae, between the two last-mentioned, a mutually synergistic relation was supposed to exist, while the two other sides of the triangle represented reciprocal inhibitory actions. It was not founded upon any very impressive assemblage of experimental data, it obviously left out of count members of the endocrine system whose importance is now more generally recognized, and it gave no explicit suggestion of the nature of the antagonisms and synergisms postulated.

From a purely theoretical standpoint, we may recognize that there are three entirely different mechanisms possible, each of which may lead to one hormone appearing to act as an antagonist to some other hormone. In the first place, the two hormones might react chemically with one another, as an acid reacts with an alkali, to their mutual destruction, so that chemically-equivalent amounts of the two hormones, administered together or secreted simultaneously, would exactly cancel out, with unequal mixtures, the physiological effect would be determined by the difference in the amounts of the two hormones, and could be calculated by subtraction.

In the second place, the two antagonistic hormones may act upon the same responsive tissue, but produce therein opposite or at least incompatible reactions. Arguing by analogy from the few instances that have received satisfactory study, by Clark,² Gaddum,³ and others, we may regard it as probable that in such a case the physiological effect of combined action is to be calculated, not by subtraction, but by division, that is, that it depends, not on the difference, but on the ratio between the two substances.

There is yet a third possibility: one hormone may act upon the endocrine source of some other hormone, so as to inhibit its activity, and decrease the rate of secretion. This may also give rise to an apparent antagonism, which may be physiologically or clinically conspicuous but will tend to disappear in experiments of the pharmacological type in which both the active principles are introduced in known amounts. The action of any one hormone upon some other endocrine gland may be direct or indirect, it may take place by the mediation of the nervous system, or of some third endocrine gland whose participation in the process may easily escape notice.

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

From the Department of Biochemistry, McGill University, Montreal

It is easy to see that these are three fundamentally different types of antagonism, and that there are three analogous and parallel different types of synergistic action, all theoretically possible. Diagrams such as that set up by Eppinger, Falta and Rudinger make no attempt to distinguish between these three possible types of antagonism, or of synergism, but today we are dissatisfied with such vague positions, since in many instances the nature of the observed antagonistic and synergistic effects has been more or less fully elucidated.

No examples of the first type of interaction between hormones have been established, and it does not at present seem probable that direct chemical reaction between different hormones occurs in the body. It was formerly usual to speak of the relation between the characteristic male and female sex hormones in such terms, but it is now clear that such a view is physiologically untenable and, at least for androsterone and the estrin group, chemically impossible.

The second type of interaction is well exemplified by the ovarian hormones estrin, the follicular hormone, on the one hand, and the corpus luteum hormone, progesterin, on the other. Both act upon the same group of responsive tissues, in the uterus, the vagina, and the mammary glands, in some cases, or in some circumstances, their actions are incompatible. The enormous difficulty of obtaining the characteristic vaginal response to estrin in the presence of an active corpus luteum is well known, and the suppression of the usual uterine responses to progesterin (progestational proliferation, sensitization to trauma) by administration of estrin has been described many times. On the mammary gland, however, these two hormones have similar or complementary effects. Even in the case of a single tissue, the endometrium of the rodent uterus, the two hormones may be in some respects antagonistic and in others synergistic. This tissue, when sensitized by a relative excess of progesterin, responds to certain types of trauma by the formation of a large mass of decidual cells, the deciduoma of Loeb⁴, this reaction can be prevented by the administration of estrin. A tumor-like mass of quite different, conspicuously hydropic character may develop, in response to the trauma of slitting in the presence of both estrin and progesterin⁵. In the formation of this type of tumor, which has been called the endometrial mole, progesterin appears to reinforce and enhance the action of estrin, whereas, in the formation of the deciduoma type of tumor, from the same tissue, estrin inhibits the action of progesterin.

Endocrine interrelations of this type may be exceedingly complex. Thus the glycogen-storing cells of the liver are influenced by insulin, adrenalin, the thyroid hormone, probably the hormone of the adrenal cortex, and possibly a hormone of the anterior pituitary, nor are they indifferent to less specific changes in the composition of the blood supplying them, such as changes in hydrogen-ion concentration and sugar concentration. It is obvious that so tangled a skein is not easily unravelled, and that the effect upon the liver glycogen of treatment with an anterior pituitary extract

(which may have a direct action, but is likely also to affect the thyroid and the adrenal cortex and to act upon metabolism in various ways both direct and indirect) is not easily interpreted

Such discussions lead naturally to a survey of the third type of endocrine correlation—the effects, stimulating or inhibitory, that a hormone may have upon some other endocrine gland. The most familiar, and undoubtedly most important instances are the dependence of the thyroid, the gonads, and the adrenals upon the anterior pituitary. It is well known that hypophysectomy leads to an almost complete cessation of activity, and to striking atrophic changes, in these dependent organs, and that these effects of hypophysectomy may be corrected, temporarily at least, by replacement therapy with suitable pituitary extracts. Moreover, the anterior lobe itself is affected by changes in the activity of these dependent organs, the gonads, the thyroid, and (probably) the adrenal cortex. It is certain that these reciprocal relationships between certain glands and the anterior pituitary play a predominant part in the correlation of the endocrine system, and they cannot be passed over thus briefly.

In the meantime, however, it is interesting to note that while the importance of these pituitary correlations is ever more widely appreciated and applied in interpretation, there are relatively few other instances of action of hormones upon endocrine glands. A number of supposed cases of this type of interrelation have been shown, by further study, to be indirect actions, or to be non-specific. Thus the fact that the normal rhythm of estrus is usually interrupted by destruction of the adrenal cortex does not indicate a direct action of the cortical hormone upon the ovaries, since it has been shown⁶ that if the general condition of the adrenalectomized rat can be satisfactorily maintained by supplying large amounts of salt, the estrus cycles continue. The anestrus after adrenalectomy is therefore the reflection of a generalized cachexia and comparable to the anestrus of starvation; it is probable that the anestrus observed in experimental hyperthyroidism is, in part at least, of similar origin and not to be regarded as evidence of a specific action of the thyroid hormone upon the ovaries. There is some reason to believe, however, that the thyroid hormone has a direct influence upon the development of the islets of Langerhans,⁷ and that the ovarian and testicular hormones cause atrophic involution of the thymus.⁸

In the above-mentioned instances the effect appears to be specific, and it is likely, though not certain, that it is direct. There are other cases in which specificity is not in question, but which must be regarded as indirect. The statement that administration of adequate doses of insulin leads to discharge of adrenalin is merely an abbreviated way of saying that the insulin usually produces a fall in blood sugar, which in turn stimulates the nervous centers controlling adrenalin secretion.⁹

Among these indirect correlations of this type, none are more interesting at the present day than those in which the anterior pituitary plays the mediating role. Before these can be discussed, it will be necessary to examine

more closely the direct linkages involving the anterior pituitary. The multiplicity of endocrine activities with which this minute gland has been credited has become almost a byword, and it is too true that some investigators, discovering some minor consequence of injections of pituitary extracts, have been uncritically rash in assuming a direct specific mechanism and postulating a new pituitary hormone. Nevertheless, the fractionation of pituitary extracts into partially-purified products has shown, by the manner in which the manifold activities of the crude original extract have been distributed among the final fractions, that the situation is extremely complex. This chemical dissection of the gland, though far from complete, already permits one to say with some degree of confidence that at least seven distinct and separable hormones are present in the crude extracts. Prolactin, which develops the crop-gland of the pigeon, and brings the developed mammary gland of the mammal into active secretion, possesses distinctive chemical properties which permit its separation from the other active principles¹⁰. Equally distinctive, though very different, are the properties of the adrenotropic hormone, assayed by its power to restore the atrophic adrenal cortex of the hypophysectomized rat¹¹. It does not seem possible to doubt that there are two active principles affecting the ovary, one primarily follicle-stimulating and one promoting luteinization^{12, 13}. The thyreotropic hormone, which causes hyperplastic changes in the thyroid gland and increased secretory activity in susceptible animals, may be separated from the foregoing¹⁴. The ketogenic principle, which in some unexplained but probably direct manner intervenes in metabolism to cause an accumulation of acetone bodies in the blood, is found to be distributed among various fractions in such a way that it cannot be identified with any of the other accepted hormones¹⁵. The growth hormone may be obtained reasonably free from the others¹⁶. Beyond this it does not, at present, seem profitable to go. It has already been hinted that the principles above mentioned can, in so many different ways, play a part in carbohydrate metabolism, that the existence of a specific hormone acting directly thereon is very hard to establish, if such a substance exists, it is hard to separate from the growth hormone. A dependence of the parathyroids upon the anterior pituitary seems rather clear in some species,^{17, 18} but the evidence for a specific pituitary hormone with a direct action on the parathyroids¹⁹ is relatively scanty. Other postulated pituitary hormones rest upon still more slender bases.

The importance of the anterior pituitary in endocrine correlations is only in part due to the fact that its hormones control other endocrine glands, it is also partly due to the fact that these glands reciprocally influence the anterior lobe. This aspect of the question has been studied in three somewhat different ways. In the first place, histological changes or gross changes in the anterior lobe may be noted after the ablation of some endocrine gland or after the administration of some endocrine principle. The existence of an effect may be demonstrable in this way, but the nature of the effect remains somewhat obscure. When only two pituitary hormones—growth

and gonadotropic—were recognized, it was tempting to connect them with the two chief types of granulated cells in the anterior lobe, and to interpret histological changes accordingly, but if at least seven hormones are postulated, the interpretation can hardly be carried out in detail

Secondly, the effect of various experimental procedures upon the amount of one or other of the hormones actually present in the anterior lobe may be approximately determined. The pituitaries of the experimental animals may be introduced, either as implants or as crude extracts, into suitably reactive test animals and the magnitude of the effects obtained noted. Such procedures are subject to the usual errors of the cruder methods of biological assay, and moreover the interpretation of the findings is fundamentally ambiguous. It is well known that the withdrawal of ovarian hormones by castration leads, in many species, to marked histological change and increase in size of the anterior pituitary, if the pituitaries of such castrates are implanted into immature female rats or mice, they prove to be unusually rich in gonad-stimulating principles, and there is ample additional evidence to show that the anterior lobe not merely contains large amounts of these substances, but that it secretes them in far larger quantities than usual. In this case the amount of hormone present in the anterior lobe is an index of its activity. This correlation is not inevitable. Thus it has been argued²⁰ that the anterior pituitary of the pregnant woman is deficient in gonadotropic hormones, not because it is not producing them, but rather because it is producing them so rapidly that they are not stored in the gland itself. Similarly the hyperactive thyroid gland in exophthalmic goiter contains less than the usual quantity of thyroxin²¹

Thirdly, it is in some cases possible to obtain direct evidence of the degree of the activity of the anterior lobe. The amount of the hormone under consideration present in the circulating blood may be measured, and unless the rate of destruction or of excretion of the hormone varies greatly there will be no likelihood of errors in interpretation. Thus the hyperactivity of the pituitary of the castrated rodent has been established by cross-circulation (parabiosis) experiments²² and by assays of samples of drawn blood²³. Alternatively, structural or functional changes in the animal itself may be indicative of altered pituitary function. For example, the occurrence of thyroid hyperplasia after castration may be taken to mean that the anterior lobe has increased its production, not merely of gonadotropic substances, but also of thyreotropic hormone, an interpretation supported by the finding²⁴ that the thyreotropic-hormone content of the pituitary is increased.

This last example brings the discussion back to the point from which it started—namely, that the influence of one hormone upon some other endocrine gland may take place through the mediation of the anterior pituitary. There is no doubt that this is a common occurrence in experimental studies, and it is probable that it is of great physiological importance in the integration of the endocrine system. Examples are not far to seek when the ad-

ministration of large doses of pregnancy-urine preparations stimulates the ovaries of the rat to unusual endocrine activity, there results an activation of the pituitary which in turn produces enlargement and hyperplasia of the thyroid²⁷, again, enlargement of the adrenals seen after treatment with extremely large doses of the ovarian hormone estrin²⁸ is similarly ascribable to activation of the anterior lobe to produce the adrenotropic hormone. Evidence that the pituitary does participate in these reactions is furnished by the fact that in both instances enlargement of the anterior lobe occurs to a marked degree, and also by the fact that neither effect is obtainable in animals from which the pituitary has been removed.

On the whole, it does not seem that these reactions are highly specific. The structural changes in the anterior lobe produced by thyroidectomy are somewhat similar to, though distinguishable from those produced by ovariectomy, in both cases, the thyreotropic-hormone content of the gland is increased^{24, 27}. One gains the impression that, as a general rule, the anterior lobe reacts with a generalized increase or decrease in activity to alterations in the supply of hormones from the dependent endocrine glands. If the pituitary secretes many hormones, it seems theoretically possible that it might secrete any one of them in excess and the rest in normal amounts, but it is hard to find cases in which this theoretical possibility seems to be realized in practice. Pathological hypersecretion of the growth hormone, producing acromegaly, is very often accompanied by signs of hypersecretion of thyreotropic hormone (causing elevation of the basal metabolic rate by thyroid stimulation), by symptoms of diabetes, and in some instances at least by signs of over-production of gonad-stimulating hormones. Yet this problem has not been thoroughly explored, and experimental means may yet be found whereby one of the manifold endocrine functions of the anterior pituitary may be influenced without disturbing the others.

Perhaps an instance may be found in the study of lactation. Since removal of the pituitary at any time during lactation promptly halts the secretion of milk,²⁸ it is clear that the pituitary hormone prolactin is supplied throughout the whole period, and it has been shown that the mechanical stimulation of the nipples during suckling is responsible for the maintenance of prolactin secretion²⁹. In this case it does not seem that the anterior lobe is activated as a whole, the ovaries, for instance, are quiescent—if they are experimentally roused to activity, pituitary function is affected and milk secretion fails^{30, 31}—and this might indicate that the anterior lobe, though actively producing prolactin, has ceased to secrete gonad-stimulating hormones. However, since it seems that prolactin itself has an inhibiting effect upon the ovaries,³² it is not certain that the interpretation indicated is the correct one.

This example introduces into the question of endocrine correlations the factor, hitherto omitted, of nervous links in the chain of interrelations. It seems difficult to suppose that the influence of suckling upon the pituitary is

transmitted by other than nervous routes, yet since the more obvious possible nervous pathways may be interrupted without effect, it is hard to conceive what these routes may be³⁰ The same difficulty arises in considering the sudden burst of pituitary activity which follows mechanical stimulation of the genital region in the estrous rabbit. Yet despite the difficulties, it is hard to escape the view that pituitary function is to some extent under nervous control, and is influenced by stimuli arising peripherally or originating in higher centers. It has even been suggested³¹ that the effect of hormones such as estrin upon the pituitary is indirect, and involves the stimulation of a center controlling the anterior lobe by unidentified nerve fibers, but since this view is based chiefly on failure of the usual pituitary response to estrin in transplanted (hence denervated) pituitaries, and since this organ does not lend itself well to transplantation, the question may be regarded as still undecided.

This question of the nervous control of the anterior lobe is not more difficult than the problem of nervous regulation of other endocrine organs. The adrenal medulla furnishes an unique example of an endocrine gland whose activity is quite certainly dependent primarily upon its innervation. The theory that there are true secretory fibers to the cells of the pancreatic islets remains a highly controversial and difficult topic, the same might be said of the thyroid gland. On the whole, interest in the question of nervous correlation within the endocrine system has decreased with the increase in knowledge of hormonal correlating mechanisms and especially of the central part played by the anterior pituitary.

No discussion of endocrine correlations could now be complete without some mention of the "anti-hormones." These substances, of unknown nature and origin, appear in the circulation of animals subjected to prolonged treatment with certain pituitary extracts, and are detected by their power to inhibit the action of such extracts. Our knowledge of them has been summarized elsewhere,³² and is not yet adequate to permit any evaluation of the part they play in the complex system of actions and reactions which ensures the integration and correlation of the endocrine system.

REFERENCES

- 1 EPPINGER, H., FAITA, W., and RUDINGER, C. Über die Wechselwirkung der Drüsen mit innerer Sekretion, *Ztschr f klin Med*, 1908, 146, 1-52
- 2 CLARK, A. J. Antagonism of acetyl-choline by atropine, *Jr Physiol*, 1926, 141, 547-556
- 3 GADDUM, J. H. Action of adrenalin and ergotamine on uterus of rabbit, *Jr Physiol*, 1926, 141, 141-150
- 4 LOEB, L. Production of deciduomata and the relation between the ovaries and the formation of the decidua, *Jr Am Med Assoc*, 1908, 1, 1897-1901
- 5 SELYE, H., HARLOW, C., and McKEOWN, T. Endometrial mole, *Proc Soc Exper Biol and Med*, 1935, 44, 1253-1256
- 6 KUTZ, R. L., McKEOWN, T., and SELYE, H. Effect of salt treatment in certain changes following adrenalectomy, *Proc Soc Exper Biol and Med*, 1934, 44, 331-332

- 7 FLORENTIN, P, and WATRIN, J Action de la thyroxine sur le pancreas du cobaye, *Compt rend Soc de biol*, 1931, cvii, 372-374
- 8 EVANS, H M, and SIMPSON, M E Reduction of thymus by gonadotropic hormone, *Anat Rec*, 1934, lx, 423-435
- 9 HOUSSAY, B A, LEWIS, J T, and MOLINELLI, E A Role de la secretion d'adrenaline pendant l'hypoglycemie produite par l'insuline, *Compt rend Soc de biol*, 1924, xci, 1011-1013
- 10 RIDDLE, O, BATES, R W, and DYKSHORN, S W Preparation, identification and assay of prolactin, *Am Jr Physiol*, 1933, cv, 191-216
- 11 COLLIP, J B, ANDERSON, E M, and THOMSON, D L Adrenotropic hormone of anterior pituitary lobe, *Lancet*, 1933, ii, 347-348
- 12 FEVOLD, H L, and HISAW, F L Interactions of gonad-stimulating hormones in ovarian development, *Am Jr Physiol*, 1934, cxv, 655-665
- 13 WALLEN-LAWRENCE, Z Fractionation of gonad-stimulating substance of the anterior lobe of pituitary body, *Jr Biol Chem*, 1933, c, xcvi-xciv
- 14 GREER, R O Separation of thyrotropic from gonadotropic substances of pituitary, *Am Jr Physiol*, 1935, cx, 692-699
- 15 BLACK, P T, COLLIP, J B, and THOMSON, D L Effect of anterior pituitary extracts on acetone body excretion in rat, *Jr Physiol*, 1934, lxxvii, 385-391
- 16 COLLIP, J B, SELYE, H, and THOMSON, D L Preparation of purified and highly potent extract of growth hormone of anterior pituitary lobe, *Proc Soc Exper Biol and Med*, 1933, xxx, 544-546
- 17 HERTZ, S, and KRAVES, A Parathyreotropic action of anterior pituitary, *Endocrinology*, 1934, xviii, 350-360
- 18 HOUSSAY, B A, and SAMMARTINO, R Die Epithelkörperchen bei den Hypophysen- und Pankreasinsuffizienzen des Hundes, *Beitr z path Anat u z allg Path*, 1934, xciii, 405-416
- 19 ANSELMINO, K J, HOFFMAN, F, and HEROLD, L Über die parathyreotrope Wirkung von Hypophysenvorderlappenextrakten, *Klin Wchnschr*, 1934, viii, 45
- 20 ZONDFK, B Die Hormone des Ovariums und des Hypophysenvorderlappens, 1931, J Springer, Berlin, p 213
- 21 GUTMAN, A B, BENEDICT, E M, BAXTER, B, and PALMER, W W Effect of administration of iodine on total iodine, inorganic iodine, and thyroxine iodine content of pathological thyroid gland, *Jr Biol Chem*, 1932, xcvi, 303-324
- 22 MATSUYAMA, R Experimentelle Untersuchungen mit Rattenparabiosen, *Frankf Ztschr f Pathol*, 1921, xlv, 436
- 23 EMERY, F E Anterior pituitary sex hormone in blood and urine of rats, *Am Jr Physiol*, 1932, ci, 246-250
- 24 LOFSER, A Der Einfluss des Ovariums auf die Sekretion des thyreotropen Hormons der Hypophyse, *Klin Wchnschr*, 1934, viii, 766-767
- 25 COLLIP, J B, SELYE, H, THOMSON, D L, and WILLIAMSON, J E Effect of prolonged administration of anterior pituitary-like hormone on pituitary and thyroid, *Proc Soc Exper Biol and Med*, 1933, xxx, 590-591
- 26 SELYE, H, COLLIP, J B, and THOMSON, D L Effect of estrin on ovaries and adrenals, *Proc Soc Exper Biol and Med*, 1935, xxxii, 1377
- 27 CH'EN, G, and VAN DYKE, H B Amount of thyroid-stimulating hormone in anterior pituitary of thyroidectomized rabbit, *Proc Soc Exper Biol and Med*, 1934, xxxii, 484-485
- 28 COLLIP, J B, SELYE, H, and THOMSON, D L Beitrage zur Kenntnis der Physiologie des Gehirnanhanges, *Virchow's Arch f path Anat*, 1933, ccxc, 23-46
- 29 SEIFF, H On nervous control of lactation, *Am Jr Physiol*, 1934, cvii, 535-538

- 30 SELYE, H, COLLIP, J B, and THOMSON, D L Nervous and hormonal factors in lactation, *Endocrinology*, 1934, *xviii*, 237-248
- 31 ENZMANN, E V, and PINCUS, G Effect on lactating mice of injecting extract of urine of pregnancy, *Am Jr Physiol*, 1933, *ciii*, 30-33
- 32 BATES, R W, LAHR, E L, and RIDDLE, O Gross action of prolactin and follicle-stimulating hormone on mature ovary and sex accessories of fowl, *Am Jr Physiol*, 1935, *cvi*, 361-368
- 33 HOHLWEG, W, and JUNKMANN, K Die hormonale-nervöse Regulierung der Funktion des Hypophysenvorderlappens, *Klin Wchnschr*, 1932, *vi*, 321
- 34 COLLIP, J B Recent studies on anti-hormones, *ANN INT MED*, 1935, *ix*, 150

ARTERIOSCLEROSIS AND HYPERTENSION IN DIABETES

By HOWARD F. ROOT, M.D., F.A.C.P., and THOMAS P. SHARKEY, M.D.,
Boston, Massachusetts

THAT arteriosclerosis occurs in excessive degree in diabetic patients has found general acceptance among American students. The importance of characteristic metabolic changes of diabetes in its causation was pointed out in the first study of Deaconess Hospital autopsy data by Root and Warren.¹ Further reports by Joslin² emphasized the clinical significance of arteriosclerotic complications of diabetes, and Warren³ summarized the pathologic data bearing upon arteriosclerosis in a large series of diabetics. Other aspects of this problem require investigation, such as (1) when does the excessive arteriosclerosis found in diabetic patients develop? (2) what are the characteristic steps in its progress? (3) are the morphologic changes of arteriosclerosis in diabetes different from those in non-diabetic patients? In this paper briefly are summarized the results of an analysis of the clinical records and the postmortem examinations of 175 diabetic patients at the New England Deaconess Hospital.

Fifty-four per cent of the cases had had hypertension indicated by a systolic pressure exceeding 150 millimeters of mercury. A few patients were included who had only a single blood pressure reading between 150 and 160 millimeters. A considerable number of the hypertensive group could not be said to have a constantly elevated blood pressure. Little attention was paid to the diastolic pressure although it varied from 80 to 130 in the hypertensive group and, though its more fundamental importance is conceded, no great change in the classification of the patients would have occurred by using the diastolic pressure.

The 175 cases included 100 females and 75 males, of whom 93 had a systolic blood pressure at some time between 150 and 230 mm. mercury. Obesity had been present in 87 per cent of the hypertensive and 74 of the non-hypertensive group. The average age at death was 63 years for the hypertensive group and 51.1 for the non-hypertensive group. All the children and cases under 30 years of age fell in the non-hypertensive group.

Age at Onset of Diabetes. The old concept of diabetes as a degenerative disease of old age received its death blow from the publication of data by Pincus, Joslin and White⁴ based on 9853 cases of true diabetes. They showed clearly that the frequency of onset of diabetes declined after the sixth decade. The rate for frequency of onset indicates the susceptibility to the development of diabetes and it is clearly evident from their data that

* Read at the Philadelphia meeting of the American College of Physicians, May 3, 1935.
From the George F. Baker Clinic, Elliott P. Joslin, Medical Director, New England Deaconess Hospital, Boston, Massachusetts.

diabetes is not a disease produced by senility. Actually the susceptibility to diabetes in the eighth decade of life is less than in the third decade. If vascular disease was a significant factor in producing diabetes, how would we explain the fact that 10 per cent of all diabetes begins in the first 15 years of life, and two-fifths before the fortieth year? In this series, 21 per cent of the cases among males and 17 per cent among females began before the age of 30 years. Furthermore, errors are all in the direction of postponing the age at onset. Eighteen cases died under the age of 40 years, of these, seven had had diabetes over five years, and every one had arteriosclerosis, including two boys 16 years of age, and Case No. 1794 that died at 33 years of age with coronary occlusion. None of these cases under the age of 40 years had hypertension.

Development of Excessive Arteriosclerosis For a demonstration of the difference in the extent and severity of arteriosclerosis in diabetes as compared with non-diabetics, a series of 170 non-diabetic autopsies examined at the New England Deaconess Hospital by the same pathologist was compared with this series of 175 diabetics (see tables 1 and 2). The 170 cases

TABLE I
Coronary Sclerosis in 175 Diabetics at Autopsy

Cases	93 Cases with Hypertension			82 Cases without Hypertension		
	Absent	Slight to Moderate	Advanced	Absent	Slight to Moderate	Advanced
Per cent	75	32	60	44	34	22
Age, yrs	61	61	63	43	57	57
Duration of diabetes, yrs	3	7	11	4	6	8

Note "Advanced" means marked obliteration of lumen and includes cases with old and recent gross infarction.

TABLE II
Coronary Sclerosis in 170 Non-Diabetics

Cases	Absent	Slight to Moderate	Advanced
Per cent	37	50	13
Age, yrs	58	64	66

were unselected except that no cases under 40 years of age were included, whereas in the diabetic group some 18 cases died under the age of 40 years. This difference would have the effect of handicapping the diabetic group since the older non-diabetic group would have more ordinary arteriosclerosis consistent with age. Without quoting in detail any percentages, a striking

excess of advanced arteriosclerotic lesions occurred in the diabetics. Thus, advanced coronary sclerosis with occlusion occurred in 40 per cent of the diabetics and in only 13 per cent of the non-diabetics, in spite of the fact that the diabetics averaged six years younger than the non-diabetics. Our first problem, then, was to determine whether this excessive arteriosclerosis was present when the diabetes began or whether it could be shown to have probably occurred after the onset of diabetes.

For this purpose we selected only those cases of diabetes with duration of one year or less on the assumption that diabetes of such short duration could not have produced much change in the arterial system. There were 23 such cases and in table 3 are shown the average figures. It will be seen

TABLE III
Aortic Atherosclerosis in 23 Diabetics and 170 Non-Diabetics at Autopsy

Grade of Sclerosis	Diabetes Less Than One Year in Duration		Non-Diabetics	
	Number	Per Cent	Number	Per Cent
Slight	14	61	94	55
Moderate and Advanced	9	39	76	45

that in the 23 cases, although their average age was not materially different from that of the non-diabetics, the frequency of severe arteriosclerosis in the aorta was somewhat less than in the non-diabetics. Similar results were obtained when the coronary vessels were compared. If now, cases with diabetes of long duration are examined, the contrast is striking.

Duration of Diabetes In 46 cases the duration of diabetes exceeded 10 years, the youngest case at death being 43 years of age with diabetes of 15 1/2 years' duration. The oldest case was 83 years with diabetes for 33 years. In 32 of the 46 cases hypertension had been present. Twenty-five of these 30 cases died as a result of coronary occlusion. Thus, in this group with diabetes of long duration coronary disease as the cause of death was just four times as frequent in the diabetics as in the non-diabetic control series.

Frequency of Hypertension The excessive frequency of hypertension in diabetic patients has been a matter of frequent comment. Bell and Clawson⁵ from necropsy statistics showed that 42.5 per cent of diabetics had hypertension, and they regarded hypertension as 2.7 times as frequent in diabetics as in non-diabetics. Major⁶ also regarded hypertension as more frequent in diabetes. Unfortunately it is difficult to state the relative period of onset of hypertension and diabetes in most series of cases with accuracy. In this series where accurate data were possible, it is true that diabetes preceded hypertension in the majority of cases. Recently in a review of 482 cases under observation for 10 years the blood pressure rose from normal to a level above 150 mm. mercury in 16 per cent of the cases, and in 50 per cent rose over 10 mm. of mercury.

Localization and Type of Vascular Change Aortic atherosclerosis was excessive in the diabetics in this series, in contrast with the 170 controls and in contrast with the aortic lesions in 5060 consecutive post mortems reported by Willius et al.⁷ Absence of atherosclerosis of the aorta occurred in only 7 of the 175 diabetics, and their average age was 26 years and the duration of their diabetes only 0.9 year. The difference in degree of severity is indicated by the frequency of Grade IV lesions. In Willius' series 49 such cases occurred in the 3473 over 40 years of age, or 1.4 per cent. Among our diabetics Grade IV lesions, that is with calcification and ulceration, occurred in 37 cases or 21 per cent, an incidence 15 times as great. Advanced lesions in the diabetics occurred eight times as frequently in the hypertensive as in the non-hypertensive diabetics.

Chemical differences in the aortae of diabetics and non-diabetics studied at the Deaconess Hospital were found by Lehnheir.⁸ The cholesterol content was 8.07 grams per cent in the diabetics as compared with 4.8 grams per cent in the non-diabetics. In the adult diabetic cases the average calcium content was 5.2 grams per cent as compared with 1.57 grams per cent for non-diabetics. There seemed to be a definitely increasing percentage of fatty acids with increasing atherosclerosis, although certain cases presented exceptions. The source of the lipids which appeared in the aortae is not revealed. Whether they come from the blood stream or are formed from chemical disintegration of substances in the wall of the vessels remains unproved.

Heart Disease Coronary sclerosis with the changes secondary to occlusion, either acute or chronic, was the characteristic finding in the diabetics. In the first table these findings are summarized as follows:

Coronary sclerosis was absent only in those cases where the average duration of diabetes was three years. Advanced coronary sclerosis, including only cases with occlusion of the coronary arteries, occurred in 60 per cent of 93 cases with hypertension and 22 per cent of 82 cases without hypertension, in contrast to only 13 per cent of the non-diabetic patients. The effect of duration of diabetes comes out clearly here because advanced coronary disease was twice as frequent in the diabetics as in the non-diabetics. The exceeding frequency of coronary disease in the hypertensive cases is in part related to the greater duration of diabetes and to their greater age. The striking feature of the diabetic heart is the lack of great hypertrophy except in those cases with preexisting hypertension. This failure of hypertrophy may be due to the type of pathologic change found at autopsy, and is in marked contrast to the heart of myocardial insufficiency cases associated with essential hypertension, it suggests further that the hypertension may have followed the arteriosclerotic process, accounting thus for the limitation of any constant or marked hypertrophy.

Retinal Arteriosclerosis During the present year two important reports on the eyes of diabetics have appeared, the one from the Mayo Clinic, Wagener, Dry and Wilder,⁹ and the other reporting the examinations of

2000 diabetic patients at the Deaconess Hospital by Waite and Beetham¹⁰ Both papers come to one conclusion which completely reverses the previous conceptions of retinal arteriosclerosis and its relationship to the retinal disease seen in diabetes Waite and Beetham at the Deaconess Hospital found that retinal arteriosclerosis is no more common among the diabetics than among a control series which they examined with equal care The striking difference is in the frequency of retinal hemorrhages which increase steadily with the duration of diabetes and were unrelated to blood pressure or to retinal arteriosclerosis Interestingly enough the same conclusion was arrived at independently by Wagener and Wilder who reversed their formerly expressed opinion upon this important subject It, therefore, appears clear that these two papers bring out a fundamental point of divergence Retinal hemorrhages are the characteristic feature of diabetes and are due to some specific metabolic effect exerted upon the capillaries As a result extravasations of blood occur These may be absorbed or may be organized The waxy exudates seen may be due to hyaline degeneration of these hemorrhages At any rate there is a great tendency in diabetes for fibrosis to occur with organization of the hemorrhages leading to retinitis proliferans Edema of the discs and the changes characteristic of typical malignant hypertension were not observed in any of the diabetics at the Deaconess Hospital

Peripheral Gangrene Gangrene of an extremity had occurred in 48 of the 175 autopsies In this group 32 patients had had hypertension in contrast to 16 with normal blood pressure The striking feature, however, of the arteries in the leg is the similarity in pathologic findings in both the hypertensive and non-hypertensive cases Diabetic gangrene is characteristically moist where senile gangrene is dry, owing to the fact that the changes produced by diabetes are primarily intimal and progressively occlusive in type So-called Monckeberg's sclerosis is a common type of sclerosis in the muscular arteries of the legs present in a considerable percentage of individuals after 50 years Therefore it is to be expected that the diabetic legs at pathologic examination will show medial sclerosis, but the striking difference between the diabetic and the non-diabetic is not in the media but in the degree of intimal change Here the marked localized proliferation of the intima with deposition of fatty material including cholesterol crystals is striking This process goes on slowly with gradual encroachment upon the lumen, until trauma with infection, producing swelling and closure of the small arterioles or spontaneous thrombosis, leads to gangrene In the small arterioles, obliterative endarteritis with hyaline thickening of the intima and obliteration of the lumen is the rule Hypertension seems to serve as an additional burden accentuating the process The important point is that the muscular type of arteries shows the changes produced by diabetes most characteristically

Nephrosclerosis An attempt was made to classify the degree of arteriosclerosis present in the various types of vessels in the kidneys in relation to

hypertension. It appeared that slight degrees of sclerosis were almost constantly found in the larger vessels and arterioles in the non-hypertensive group. The more advanced sclerotic changes in the larger vessels and in the arterioles, however, were more frequent in the hypertensive group. Hyalinization of the glomeruli was found about 1.5 times as frequently in the hypertensive as in the non-hypertensive group. Fibrosis of the glomeruli was reported almost three times as frequently in the hypertensive as in the non-hypertensive group. Intimal changes as noted elsewhere were most frequently found in the larger vessels. Cases classified as moderate to marked renal arteriosclerosis exhibited advanced vascular lesions elsewhere including coronary thrombosis, peripheral gangrene, cerebral thrombosis and hemorrhage, and all but one case showed marked to extreme aortic atherosclerosis with calcification. No case in our series died primarily of uremia, despite occasionally advanced degrees of nephrosclerosis. Renal insufficiency, when it occurred, was secondary to cardiac failure.

Pancreas and Spleen The vessels of the pancreatic-splenic circuit revealed less constant and less easily interpreted findings. The control series studied by Warren³ showed as high an incidence of pancreatic arteriosclerosis as the diabetics. Since then 83 cases have been added to the autopsy series at the Deaconess Hospital and in only 9.5 per cent of these was any serious pancreatic arteriosclerosis recorded. Hyalinization of the islands of Langerhans occurred independently of arteriosclerosis and was associated with the relatively mild type of diabetes. The frequency with which arteriolar sclerosis of the pancreatic vessels is observed in essential or malignant hypertension would lead one to expect a relatively high incidence of diabetes in these cases. This is not substantiated by autopsy reports of hypertensive cases. Bell and Clawson⁶ state that only 5.5 per cent of the hypertensive cases over 50 years of age have diabetes. Murphy¹¹ in his series of autopsies of cases of hypertension found arteriosclerosis in the pancreas to parallel uniformly that in the kidneys. In a personal communication Murphy states that only 14 out of 352 cases had diabetes. This, in view of the age of the patients, he considered a low incidence. No good evidence exists for believing that arteriosclerosis of the pancreas plays any considerable part in the causation of diabetes.

In the spleen arteriosclerosis was present in 32 per cent of the hypertensive cases and in 26 per cent of the non-hypertensive cases. Arteriosclerosis was present in 31 per cent in the hypertensive group and 31 per cent in the non-hypertensive group. The somewhat greater frequency of this condition in the splenic vessels in hypertension was not marked. Conclusions drawn from the occurrence of vascular sclerosis of splenic vessels are of doubtful value.

Discussion Although our chief purpose is to present facts regarding the arteriosclerotic lesions in diabetes, contrasting the hypertensive and non-hypertensive cases, some discussion of their theoretical bearings may be permitted. First is the excess of arteriosclerosis in the coronaries, aorta and

legs in these diabetics as compared with control series of non-diabetics. Second is the fact that among 175 diabetics followed to death hypertension occurred in 54 per cent. Third is the occurrence of all the characteristic vascular lesions of diabetes (retinal hemorrhages, coronary occlusion, gangrene) in diabetics without hypertension as well as in cases with hypertension. The existence of hypertension cannot be considered a *sine qua non* of these complications. Fourth, the incidence of these vascular complications was greater in the hypertensive group, as if hypertension acted as an additional factor increasing greatly the tendency to such lesions. This conclusion must be qualified by consideration of the greater average age of the hypertensive group. The common observation in a diabetic clinic of hypertension developing as time goes by in cases previously non-hypertensive is not to be dismissed too readily as due merely to the natural incidence with increasing age. Fifth, the association of large vessel arteriosclerosis constantly whenever arteriosclerosis was present suggested that changes in the large arteries occurred first.

In considering the etiology of arterial hypertension it has become customary to divide the possible agents under five heads: (1) circulating substances, including hormones, (2) the influence of the nervous system, (3) the structural changes in the vascular system, (4) infections and allergy, (5) constitutional factors. For careful reviews the articles of Meakins, Durig and Weiss may best be consulted. The rôle of the nervous system in the regulation of blood pressure is outstanding. The sympathetic vasomotor system with its constrictive influence is counterbalanced by the activity of the parasympathetic vasomotor nervous system particularly through depressive reflexes. An increase in the pressor mechanism or hypoactivity of the depressor reflexes has been offered as a cause. There is no clear evidence in our cases of unusual psychic or nervous make-up on which to base the theory that hypertension occurred first and vascular disease followed. Similarly the rôles of infections and allergy lack support. It is true that in diabetes, infections of the kidneys are common and that hypertension may follow such infections. Somewhat more reasonable is the theory that the spotty lesions of arteriosclerosis represent the results of low-grade and repeated bacterial invasion or degeneration due to bacterial toxins. However, no one holds the larger arteries responsible for hypertension. One would have to assume that the infections cause a different reaction in the smaller arterioles.

The rôle of inherited constitution has been emphasized in relation to hypertension. Although nervous and psychic factors, vascular changes of senescence, infections and toxins contribute, they seem to be most effective in certain individuals who may have inherited certain anatomical and functional characteristics of the nervous and vascular systems. O'Hare, Walker and Vickers¹² obtained a history of vascular disease in 68 per cent of a group of patients with arterial hypertension. Weitz¹³ concluded that hypertension is inherited as a dominant characteristic. On the negative side Benedict and Root¹⁴ studied a man 92 years of age who showed little evi-

dence of arteriosclerosis and a normal blood pressure. His family history contained no deaths from vascular disease before the age of 75 years. That the predisposition to diabetes is inherited as a Mendelian recessive characteristic has received support from the studies of Pincus and White¹⁵. Possibly a tendency to vascular disease is also inherited in the diabetic, but it is significant that excessive arteriosclerosis only occurred after the onset of diabetes in our series.

The influence of circulating metabolites in the blood and anatomic changes in the vessels themselves can hardly be separated. So far as arterial hypertension is concerned, the rôles of glucose, salt, guanidine, the potassium-calcium ratio and of peptones in the blood are still not clearly defined. The effects of circulating hormones from the pituitary and adrenals, while definite, do not seem to explain more than a small portion of the cases. Other substances, such as cholin and cholin compound, histamine and pancreatic extracts, such as "padutin," have temporary effects upon blood pressure. The one substance found both in the blood and in the blood vessel walls with which, experimentally, typical atherosclerotic lesions can be produced is cholesterol. It is sometimes found in increased amounts in cases of hypertension. Duing points out that it is not the height of the cholesterol in the blood, but the degree of saturation which is important. In hypertension the serum is often over saturated with cholesterol even though concentration in milligrams per 100 c.c. is normal. Thus it is the relation between the cholesterol and the colloids of the serum together with the affinity of the cells of the arterial wall for cholesterol which determines the deposition.

Alvarez and Neuschlosz¹⁶ believe that the arterial wall with marked absorption of cholesterol has a higher contractibility and the muscles of the arterial wall are thus sensitized to adrenalin. However, medial hypertrophy, such as would be expected with continued adrenalin stimulation, was not found in this series. The structural change in the walls of both arteries and arterioles in our diabetics is the outstanding feature. The changes in the younger cases, with relatively shorter duration of diabetes, are found in the aorta and larger arteries. Hypertension develops with increased resistance of the arteriolar bed caused by a narrowed arteriolar system. Arteriolar disease never occurred without advanced changes in the larger vessels as well. That increased arteriolar resistance is due to cellular and structural change rather than to spasm from nervous origin seems most reasonable.

Leary¹⁷ has compared experimental atherosclerosis in rabbits with human coronary atherosclerosis. He points out that atherosclerosis forms 90 per cent of the important arteriosclerosis in human beings and that the coronary arteries, because they are of relatively simple structure, muscular in type and poor in elastica, afford the best field for observation of the process. The coronary arteries possess a buffer layer of muscle and cellular subendothelial fibrous tissue which differ from other muscular arteries. It is without a circulation of its own and depends upon imbibition. These arteries, be-

cause of their anatomical relationship, are subject to great strain, meeting high pressure from the blood-filled aorta and resistance from their compressed intramural branches which are closed during the muscular systole of the heart. Relatively they might be compared with the muscular arteries of the legs of diabetic patients which have been subjected to unusual strain because of the almost universal obesity of most diabetic patients. Leary finds that the characteristic lesion induced with atherosclerosis of coronary vessels is fibrosis associated with the presence of lipid cells. In older age periods there are large accumulations of lipid cells with very little accompanying connective tissue. As a result of poor nutrition massive necrosis occurs causing the so-called "abscesses." In the young adults, therefore, the standard cause of death is thrombosis following subendothelial necrosis. On the other hand, in the older group a rupture of the abscess occurs in the lumen of the artery followed by thrombosis. The process is primary in the intima. Lesions in the elastica and media occur secondarily.

Leary was able to reproduce the lesions accurately by the feeding of cholesterol to rabbits, and he points out that such lesions do not occur spontaneously in rabbits. The lesions produced varied in different animals in their extent and severity. This variation was comparable to the differences exhibited by human beings. In fact, he could produce all the stages of human atherosclerosis in the coronary arteries in the rabbit. He points out that eggs and milk, the most common sources of cholesterol, are really intended as foods for the infant or embryo. Man is the only animal that eats both eggs and milk throughout his lifetime and is the only animal that dies in early life from coronary sclerosis. He emphasizes the analogy with diabetes. Sugar is soluble and combustible, whereas cholesterol is not combustible, is difficult to excrete and tends to be stored. Various idiosyncrasies to cholesterol exist. An inherited poor metabolism of cholesterol is associated with an early death from coronary sclerosis. In diabetes with advancing age there develops an inefficiency of the cholesterol metabolism and more advanced arterial disease.

Our own view is that the premature and excessive development of vascular disease occurs predominantly in muscular arteries under the greatest physical strain, especially in obese patients, and is due to the metabolic changes of diabetes. The coronary and leg arteries are chiefly involved although changes in the arterioles are also found. The necessity of insulin in the glycogen metabolism of muscle and especially for the completion of the lactic acid cycle must be of some significance in this connection although the details are as yet undemonstrated. The importance of the disordered lipid metabolism, more easily demonstrated by present chemical and pathologic methods, is better understood. Hypertension then is an important contributing factor in the clinical course of the disease because it imposes additional strain, even when the patient has lost his obesity, and accentuates greatly the vascular changes in coronary and leg arteries. A further suggestion as to the metabolic factor in the arteriosclerosis of diabetes is the

fact that with modern treatment with insulin and diet more normally balanced, the frequency of arteriosclerosis in the legs of diabetic children is diminishing. The objective in the future should be the earlier possible diagnosis of diabetes and its more aggressive treatment. The final explanation will take full cognizance of the interrelationship of the endocrine glands, of the parts played by preexistent obesity, by infections, especially of the kidneys, and by inheritance.

REFERENCES

1. ROOT, H. F., and WARRREN, S. A clinical and pathologic study of 26 cases of diabetes, *Boston Med and Surg Jr*, 1926, cxciv, 145-153.
2. JOSLIN, E. P. Arteriosclerosis in diabetes, *ANN INT MED*, 1930, iv, 54-66.
3. WARREN, S. The pathology of diabetes mellitus, 1930, Lea and Febiger, Philadelphia, p. 119.
4. PINCUS, G., JOSLIN, E. P., and WHITE, P. The age-incidence relations in diabetes mellitus, *Am Jr Med Sci*, 1934, clxxviii, 116.
5. BILL, G. T., and CLAWSON, B. J. Primary (essential) hypertension, study of 420 cases, *Arch Path*, 1928, v, 939-1002.
6. MAJOR, S. Blood pressure in diabetes mellitus, a statistical study, *Arch Int Med*, 1929, xlv, 797.
7. WILIUS, SMITH, and SPRAGUE. A study of coronary and aortic sclerosis, incidence and degree in 5060 consecutive postmortem examinations, *Proc Staff Meet, Mayo Clinic*, 1933, viii, 140.
8. LEHNHERR, E. Arteriosclerosis and diabetes mellitus, *N Eng Jr Med*, 1933, ccviii, 1307.
9. WAGENER, DRY, and WILDER. Retinitis in diabetes, *N Eng Jr Med*, 1934, ccxi, 1131.
10. WAITE, J. H., and BEETHAM, W. C. The visual mechanism in diabetes mellitus (a comparative study of 2002 diabetics, and 457 non-diabetics for control), *N Eng Jr Med*, 1935, ccxii, 367.
11. MURPHY, GRILL, PESSIN, and MOYON. Essential (primary) hypertension, clinical and morphological study of 375 cases, *ANN INT MED*, 1932, i, 31.
12. O'HARE, J. P., WALKER, W. G., and VICKERS, M. D. Heredity and hypertension, *Jr Am Med Assoc*, 1924, lxxviii, 27-28.
13. WITZ. Zur Aetiologie der genuinen oder vascularen Hypertension, *Ztschr f klin Med*, 1923, xvi, 151-181.
14. BENEDICT, and ROOT. The physiology of extreme old age, *N Eng Jr Med*, 1934, ccvi, 521.
15. PINCUS, G., and WHITE, P. On the inheritance of diabetes mellitus. II. Further analysis of family histories, *Am Jr Med Sci*, 1934, clxxviii, 159.
16. ALVAREZ and NEUSCHLOSZ. Untersuchungen uber das Blutcholesterin bei arteriellem Hochdruck, *Klin Wchnschr*, 1931, x, 244.
17. LEARY. Experimental atherosclerosis in rabbit compared with human (coronary) atherosclerosis, *Arch Path*, 1934, xvi, 453-492.

THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM" AND ARTHRITIS; REVIEW OF AMERICAN AND ENGLISH LITERA- TURE FOR 1934

By PHILIP S. HENCH, M.D., *Rochester, Minnesota*, WALTER BAUER, M.D.,
F.A.C.P., *Boston*, A. ALMON FLETCHER, M.D., *Toronto*, DAVID GHRIST,
M.D., F.A.C.P., *Los Angeles*, FRANCIS HALL, M.D., F.A.C.P., *Boston*,
and T. PRISTON WHITE, M.D., *Charlotte, North Carolina*

CONTENTS

Introductory

General incidence and occupational distribution

Diseases of joints related to trauma

Diseases of joints due to infection of known type

Gonorrheal arthritis

Tuberculous arthritis

"Tuberculous rheumatism"

Pneumococcal arthritis

Scarlatinal arthritis postscarlatinal rheumatism

Syphilitic diseases of joints

Undulant fever

Haverhill fever, erythema arthriticum epidemicum

Septic (purulent) arthritis

Arthritis of subacute bacterial endocarditis

Meningococcic arthritis

Rheumatic fever

Chronic arthritis

Introduction and terminology

General remarks on etiology

Differentiation—clinical, pathologic, and radiologic

1 Atrophic arthritis

2 Hypertrophic arthritis

3 Backache and sciatica

4 Spondylitis

Atrophic and hypertrophic types

"The Facet Syndrome"

Gout and gouty arthritis

Hemophilic arthritis

Psoriatic arthritis

"Allergic," "metabolic," and "endocrine arthritis"

Diseases of muscles and fibrous tissues

Miscellaneous conditions

Physiology of articular structures

* This report constitutes the second "Rheumatism Review" prepared at the request of the American Committee for the Control of Rheumatism. The editorial comments express the opinion not of the American Committee but of the authors, a subcommittee, of which Dr. Hench is chairman. The first review covered the American and English literature on rheumatic diseases for 1932 and 1933, and appeared in the ANNALS OF INTERNAL MEDICINE last year.

IN THE last century the patient who had articular disease presented no very complicated problem to his physician. The patient's whole body was probably not examined, his joints may or may not have been. But the diagnosis was easy. His story told the tale—he simply had "rheumatism." The treatment was equally simple—salicylates.¹ The current equivalent of salicylates was likewise probably prescribed to the man of the Old Stone Age whose arthritic fossil is now a museum piece, or to the patient who had arthritis deformans and whose case is described in a medical papyrus written in Thebes about 1550 B C.²

The problem of "rheumatism" began to be complicated only when it became the subject of the intensive researches of the past few decades. The complexity of the situation is, unfortunately, not simplified by the international appearance, at too frequent intervals, of new classifications for rheumatic diseases—classifications too often the "arbeit" of one who feels that only thereby can he attain recognition as a specialist for rheumatism. Through the multiplicity of suggested nomenclatures and the profusion of publications on all phases of the problem, however, definite progress is discernible. By continued international study and cooperation the complicated problem will eventually regain, indeed is now regaining, a certain simplicity of a more enlightened type. As van Breeman, Secretary of the Ligue Internationale Contre le Rhumatisme, expressed it, the problem of rheumatism is a diamond with many facets. He who views it through only one facet will gain a totally different impression of its nature than will he who regards it exclusively from another angle. But he who will view it through many facets, and see it whole, will find the complicated becoming simple again. For after all, in the last analysis the diamond has the simple formula of carbon.

GENERAL INCIDENCE AND OCCUPATIONAL DISTRIBUTION

The incidence of rheumatic diseases is apparently increasing. This is in part attributable to the fact that more individuals are living to the ages when chronic rheumatism is most prevalent. The survey by Bigelow and Lombard revealed that in the State of Massachusetts, of the total population more than 40 years of age one person in every 10 had "rheumatism." Eighty-three per cent of all patients who had chronic rheumatism, using the term in its broad sense, were between the ages of 40 and 80 years. After the age of 40 years the disease increased with each decade, so that of persons between 70 and 80 years of age, one out of every four was notably afflicted thereby.²

[These statistics pertain to those who actually complain of the disease. The roentgenographic and pathologic studies of others (Garvin, 1927, Keefer and Myers, 1933, Bauer and Bennett, 1933) revealed that actually from 90 to 100 per cent of all persons more than 45 years of age have some type of articular disease, chiefly of the degenerative (senescent, hypertrophic, osteo-arthritic) type which, however, according to Keefer and Myers is symptomatic in only about 7 per cent of cases.—Ed.]

In the State of Connecticut (population 1,655,000) about 50,000 people have chronic rheumatism, of whom about 2,000 are probably completely disabled thereby, confined to bed or chair, needing the constant care of others. So Lombard² has estimated, if the percentage incidence in Connecticut is equal to that in Massachusetts. The disease is 12 times as prevalent as cancer but only one-fortieth as fatal. Were death the end result, everyone would fear it more. Regardless of its relatively low mortality it must be taken seriously. Any disease which carries a 10 per cent morbidity among persons who have passed the age of 40 years warrants the greatest attention.

Invalidism from rheumatic diseases is increasing in Sweden also. Edstrom³ studied its incidence among 3,500 communal workers of Gothenburg between the years of 1928 and 1932. Rheumatism accounted for about 12 per cent of all disability from sickness in this group. Comparing figures for 1932 with those for 1922, it appears that the amount of invalidism has about doubled in 10 years.

Why is it that one person falls a victim to rheumatism while another escapes? To some extent the answer may be found in studies on its incidence in certain occupations. Edstrom found rheumatic disorders much more frequently among outdoor workers (policemen and workers on trains and roads and in harbors and shipyards) than among those working indoors, as in factories.

[These statistics approximate those of Danischevsky, of Kahlmeter, and of Templaar and van Breeman⁴—Ed.]

Of three major factors—infection, constitution, and external conditions—which determine the course in a case of chronic rheumatism, Edstrom expressed the belief that the components of the latter factor (housing and working conditions, climate, environment) are most important. Were an acutely affected person able from the onset of his illness to be placed under good hygienic circumstances, the disease might often be prevented from becoming chronic. Poor housing conditions and exposure to the vicissitudes of weather may be more important etiologic factors than infection, and more worthy of correction.

Rheumatism is more prevalent in rural than in urban communities, according to the Massachusetts survey². Among persons whose economic status was poor the incidence was nearly twice as high as that among the well-to-do. More of those living in damp houses, than others, had the disease. It is probable that the relationship between poverty and rheumatism is attributable to environmental influences. The poor are unable to have as good a diet as the wealthy. They cannot afford good dentistry or early eradication of foci of infection. They are less protected from fatigue and malnutrition, from endocrine deficiency and from faulty digestion and excretion, chief predisposing causes of the disease. In Massachusetts four-fifths of the poor and about half of the well-to-do patients were not under the care of physicians.

The Factor of Predisposition To some, data of the type just noted seem devoid of real value. Thus, Climie⁵ has expressed the opinion that the masses of statistics relating to climate, housing, geographic soil, nourishment of the patient, and so forth, do not lead anywhere. The patient himself is lost sight of, a study of his internal milieu is more important than one of his external environment. What of the patient's own soil? Is there, in truth, a rheumatic diathesis, a fundamental inherent peculiarity of the person who will have rheumatism "which, granted the right coincidence of circumstances, evidences itself by that individual suffering an attack of rheumatism, the degree of illness or extent of body tissue involved depending (only) partly on the activating agent and partly on the state of preparedness of the individual, or in other words, upon his mental and physical condition at the time of the attack?" Adamson⁶ agreed that study of the soil of the person who will have rheumatism or of the victim is an inquiry long overdue. "Much stress has been laid on the nature of the rheumatic attack, perhaps not enough on the resistance of the individual and his tissues. Let us (hereafter) regard the state of the infected tissues even more than the nature of the infective agent."

[Although studies on the patient's soil are being properly demanded with increasing frequency, investigators are slow to accept the challenge. Studies on the physiology of normal joints and on the immunologic and physicochemical status of normal persons, as well as those of rheumatic and "pre-rheumatic" individuals, are meager. To a large extent they await advances in knowledge of general immunity and development of new methods for demonstration of alterations therein. The few current reports on the chemistry and cytology of blood and tissues which are available are reviewed later in this article—Ed.]

CLASSIFICATION OF DISEASES OF JOINTS AND RELATED STRUCTURES

Discussions of the various rheumatic diseases—those of joints and related structures—are arranged as in last year's review.⁴ The scheme of classification is repeated: (1) those attributable to trauma, (2) those attributable to infections of known type, (3) those possibly, or probably, attributable to infection or related toxins, for example, rheumatic fever, atrophic (infectious, proliferative, rheumatoid) arthritis, (4) those of which the chief characteristic is degenerative change in tissue, for example, hypertrophic (senescent, degenerative, osteo-) arthritis, (5) those of which the chief, or only obvious characteristic is some recognizable, or suspected, chemical derangement—a none too well defined group which includes forms of arthritis commonly called "chemical," "metabolic," "allergic," "endocrine," and (6) a miscellaneous group of unclassifiable types. Fuller details and criticism of such a classification will not be repeated. The reader is referred to the first review.⁴

DISEASES OF JOINTS RELATED TO TRAUMA

Etiologic and Clinical Considerations Traumatic arthritis may result from acute (exogenous, extrinsic) trauma, such as that from falls, blows,

accidents, or from chronic trauma incident to the abnormal use of joints in connection with occupation, recreation, obesity or poor posture. In the former variety symptoms arise, as a rule, rather suddenly. In the latter type, in which endogenous or intrinsic trauma is operating, symptoms may develop so slowly that their connection with chronic trauma may be overlooked. O'Connor's⁷ experience is that of others, that in such cases articular lesions may be well advanced without symptoms being noted until some unusual strain is superimposed on changes already present.

An acute injury to any articular component may be followed by minor symptoms and complete healing or by the production of traumatic arthritis with chronic disability. In two cases observed by Key,⁸ contusions of articular cartilage led first to acute, then to chronic, monarticular, progressive arthritis unrelieved by conservative treatment. Because of continued pain and stiffness Key explored the knees. In each case a single, small, irregularly rounded mass of fibrillating, degenerating, necrotic cartilage was found. Synovial proliferation and villus formation were present, also several small, compact collections of round cells.

[These collections, seen in Key's photographs, seem to resemble those which Allison and Ghormley, 1931, considered specific for atrophic arthritis. Recently Fisher (1935) expressed the opinion that the lymphocytic collections of Allison and Ghormley were similar to those found by him (1929) in a minority of cases of atrophic arthritis. It should be noted that Fisher now speaks of those he described as perivascular. Those noted by Allison and Ghormley were not perivascular. Recent unpublished studies of Ghormley and Deacon strengthen their opinion of the specificity of non-perivascular round-cell collections for atrophic arthritis.—Ed.]

There are, according to Jepson,⁹ four classes of traumatic backache (1) when trauma affects a patient who already has arthritis of spine or pelvis, (2) when trauma affects only soft parts of the back, such as muscles, tendons, and ligaments, (3) when patients, because of faulty posture, have a predisposition to injury, and (4) when patients are affected by occupational strain. In Jepson's 50 cases of traumatic backache, injuries to the lumbar portion of the spinal column were most common, to the cervical portion, less frequent, and to the thoracic portion, which is the least flexible and least liable to injury, infrequent. Jepson reviewed the technic and significance of various tests used to localize injury or disease of the spinal column or pelvis and to distinguish between real and fictitious pain. Smith-Petersen's and Gaenslen's procedures, the Laquer sign, Yergason's chair test, and forcible compression of the sacro-iliac joints.

Laboratory Data Roentgenograms in traumatic arthritis may be negative or may reveal a variety of alterations: capsular distention from synovial exudate in early cases, destructive and proliferative changes in cases wherein acute trauma is followed by chronic progressive arthritis.^{9, 10}

The cell count of normal synovial fluid is as follows: total number of cells per cubic millimeter, ± 50 , polymorphonuclears ± 5 per cent, mesothelial cells ± 3 per cent, monocytes ± 58 per cent, clasmatoocytes ± 30

per cent Forkner (1930) was not sure whether lymphocytes are present or not In two cases of traumatic arthritis the cytology of synovial fluid was found by Keefer, Myers and Holmes¹¹ to be as follows total cell count per cubic millimeter, 4,800 and 3,550, polymorphonuclears 94 per cent and 10 per cent, lymphocytes 3 per cent and 2 per cent, monocytes 0 and 42 per cent, clasmatocytes 3 per cent and 46 per cent

[Counts on these two cases are noted because so few have been made in cases of traumatic arthritis—Ed]

Treatment Conservative treatment consists of rest, supports or bandages, physiotherapy and graded exercises A high percentage of Jepson's⁹ patients who had traumatic backache recovered under his program which is outlined in detail When conservative treatment fails, as occasionally it does, a fusion operation may be indicated

Slight posttraumatic effusion in knee joints may be disregarded When significant, the effusion may be reduced by application of compression bandages in conjunction with physiotherapy When distention from fluid occurs recurrently, as a late sequel to injury of a knee, Glissan¹² reported that adhesions or weakened control by quadriceps muscles generally were found

When arthritis follows contusion of articular cartilage, Key expressed himself in favor of excision of the degenerating cartilage At first he hesitated to do this because his experimental resection of rabbits' cartilage generally had resulted in progressive arthritis However, similar experiments by him on dogs and cats, and by Bauer and Bennett (1933) on rabbits, were not attended by arthritis unless postoperative patellar displacement occurred Therefore, in his two cases, Key excised the injured cartilage and part of the affected synovia The knees became asymptomatic⁸

GONORRHEAL ARTHRITIS

In some cases articular complications of gonorrhea subside rapidly and completely in the course of treatment for the local infection, with or without special therapy for the joints In many others the articular disease becomes progressive, producing marked destruction and limited motion The varieties of articular involvement are of the acute type, (1) arthralgia, (2) acute synovitis, (3) acute non-purulent arthritis (serofibrinous exudate) and (4) acute purulent arthritis, of the chronic type, (1) synovitis (2) arthritis Additional forms of "gonorrheal rheumatism" are tendinitis, myositis, and keratoderma blenorrhagica (with arthritis) The patient's resistance, the virulence of the particular bacterial strain infecting him and the type of treatment used, determine the type of articular disease and the prognosis of the latter Several interesting studies on various phases of gonorrheal arthritis are current

Clinical Data Of 69 cases of gonorrheal arthritis studied by Keefer

and Myers¹³ 58 of the patients were males and 11, females. Their ages varied from 18 to 70 years. The time between the onset of the primary gonorrheal infection and the arthritis could not always be determined because of the presence, in some cases, of old infections of the genito-urinary tract of indeterminate duration, reinfections, or the appearance of exacerbations in the genital tract. Joints became involved generally within 10 to 21 days after the initial infection, in three cases, within two to six months thereafter, and in one, simultaneously with the initial infection. In three cases evidence of local gonorrhea had disappeared. It is again pointed out that polyarticular invasion (present in 60 cases, or 87 per cent) is more common than monarticular involvement (present in nine cases, or 13 per cent). Any or many joints may be attacked, but knees, ankles, and wrists were most frequently involved, hands, shoulders, and feet, less often. Heels were affected in only seven cases, a sternoclavicular or a costosternal joint, in two cases.

[A chill is often an early symptom. An acute migratory polyarthritis or polyarthralgia which recedes in favor of an acute and more stubborn monoarthritis is a feature of many cases, and one of considerable diagnostic significance.—Ed.]

Tenosynovitis often accompanied involvement of ankles or wrists. In 33 cases it was the feature which dominated the clinical picture. Tendon sheaths most frequently affected were those about the internal and external malleoli, and those over the dorsum of hands and feet, less frequently those about knees, palms, or heels were affected.

When periarticular redness, pain and thickness were marked, extensive effusions appeared and aspirations of joints yielded 40 to 165 c c of fluid. Periarticular muscular atrophy, sometimes marked, was present in all cases. Genital infections present were prostatitis in 54 cases, urethritis in 43, cervicitis in 10, epididymitis in five, and seminal vesiculitis in one. Abscess of Cowper's glands, of Bartholin's glands, and of Skene's glands each occurred once.

Temperatures of 99 to 103° F were generally present. Salicylates gave insignificant relief, a point of value in distinguishing this disease from acute rheumatic fever. The leukocyte count varied between 9,000 and 23,000 per cubic millimeter of blood, the percentage of polymorphonuclears, between 70 and 88. Sedimentation of erythrocytes was rapid in all cases, varying from 0.4 to 1.7 mm per minute (method of Erstene and O'Rourke).

Complications. In Keefer and Myers' ¹³ series, in 16 cases (23 per cent) catarrhal conjunctivitis developed, generally before, occasionally with, the arthritis. Three patients had iridocyclitis and conjunctivitis, one had endocarditis, and two had perichondritis of the cricoid cartilage, causing painful swallowing. The association with acute polyarthritis of some of these complications, especially the combination of tenosynovitis and perichondritis, may be helpful in suggesting the gonococcal nature of a case of arthritis.

Arterial thrombosis in association with gonorrhea is rare (Welch 1909) Mead and Stewart¹⁴ reported the case of a patient with acute gonorrheal polyarthritis and salpingitis After she was given 8 cc of milk intramuscularly, a general reaction culminated in peripheral arterial thrombosis necessitating amputation of three gangrenous toes Mead and Stewart found no previous record of arterial thrombosis after injections of milk and concluded that the gonorrheal arthritic infection may have induced the thrombus

[Five cases of acute thrombosis, involving the iliac, popliteal, or femoral arteries, after typhoid vaccine had been given intravenously are noted by Hensch (1932) in his list of unusual reactions to such treatment In two cases amputation was necessary Several untoward reactions to milk were also listed, not thrombosis, however It seems likely that the thrombosis in the case of Mead and Stewart may have been an unusual reaction to the foreign protein of milk and may have had nothing to do with gonorrhea —Ed]

Pathology The classification of articular complications, as noted heretofore, indicates the variety of pathologic reactions which may occur From the observations of Keefer, Parker and Myers¹⁵ on the different pathologic reactions, it would appear that the prognosis in a given case of gonorrheal arthritis depends on how severely the surface cells of the synovia are involved The pathologic reactions in knee joints were studied in two cases that came to necropsy In one case the synovial membrane was essentially normal, but the subsynovial connective tissue was markedly congested, edematous, and infiltrated with a marked cellular reaction Thus the patient presented a subsynovitis with involvement of subsynovial tissues, rather than a synovitis involving superficial synovial cell layers Gonococci were not recovered from synovial fluid In the second case the subsynovial connective tissues were not extensively involved, but the more superficial layer of synovia was markedly affected and largely destroyed Numerous gonococci were found in synovial membrane and fluid

From these comparative studies Keefer, Parker and Myers concluded that the less the superficial synovial cells are involved and the more the inflammatory reaction is confined to subsynovial or the more frankly extra-articular (periarticular) tissues, the better is the prognosis as far as preservation or restitution of function of a joint is concerned, and the less the chance of isolating gonococci from synovial fluid or tissues When "infected exudates" are present the more serious types of gonorrheal articular disease are probably present

Significance of Laboratory Data Although certain features of the clinical picture, in conjunction with an honest history, are sufficient for a presumptive diagnosis of gonorrheal arthritis, conclusive evidence should always be sought by laboratory investigations Conclusions on the value of such data, particularly smears from the genito-urinary tract, have been summarized in the first report of the Neisserian Medical Society of Massachusetts¹⁶

The Society's report included a discussion on organisms resembling gonococci, criteria necessary for a diagnosis of presumptive, as well as of proved, gonorrhea in males, females and infants, the significance of extracellular, as compared to intracellular, gram-negative organisms, and the likelihood of obtaining "negative smears" in certain cases of gonorrhea. The report is recommended to those of limited experience in this field, particularly to those faced with a doubtful case of gonorrhea or gonorrheal arthritis.

Cultures of gonococci It was the opinion of members of the society (February, 1934¹⁶) that, to date, culture of gonococci, as a routine laboratory procedure, is impracticable, and that there is no practical method for sending material to a central laboratory for culture.

[A new culture method for the identification of *Neisseria gonorrhoeae* has been recently elaborated by McLeod and his colleagues¹⁷. Its value has been confirmed by Leahy and Carpenter¹⁸ and the method has been simplified by Thompson¹⁹. Cultures are apparently simple to make and the results reliable, indeed some workers are finding them more reliable than the isolation and identification of gonococci in smears—Ed.]

Cultures of synovial fluid from 40 patients who had gonorrheal arthritis, and who were seen by Myers, Keefer and Holmes,²⁰ were positive for gonococci in only 25 per cent of the cases. Judging from pathologic studies noted in the foregoing,¹⁶ these workers believed that negative cultures or smears from synovial fluid in cases of gonorrheal arthritis result not from faulty technic but because infection is localized beneath and not on the synovial surface. As has been mentioned, when the inflammation is essentially subsynovial, and when the superficial cells of synovia are not much affected, the cell-membrane on the surface is intact, organisms do not get into the synovial fluid, and if an exudate is present it is a non-infected one. Gonococci can be isolated with ease in smears or cultures of synovial fluid only when the synovial surface membrane is the site of an intense inflammatory reaction, in such cases organisms have advanced from per-articular tissues into the cells of the synovial surface and thence into the synovial fluid, hence exudates are infected.

Complement fixation test The complement fixation (Schwartz-McNeil) test for gonorrhea is in principle similar to the Wassermann test for syphilis. Members of the Neisserian Society expressed the belief that it is of limited value—it is usually negative in cases of acute gonorrhea, for sufficient changes have not had time to occur in the blood.

[It is rarely positive during the first 10 days of infection—Ed.]

It frequently remains positive for months or years after the disease is "cured" by clinical or other laboratory standards, and false positives and false negatives may occur. A positive test, however, may serve as evidence confirmatory of other data.

According to Keefer, Myers and Holmes^{11 20} however, the test is of distinct value. The test was positive on the blood serum in 80 per cent

(45 of 55 patients¹³) to 86 per cent (37 of 43 patients²¹) of their cases of gonorrheal arthritis "at some time during the course of the disease" In about 90 per cent of these cases the test was positive on the first examination It was negative in some cases in which genital infection had been present for no longer than two weeks The test was positive on synovial fluid in from 71 per cent (17 of 24 cases²¹) to 76 per cent¹¹ In the majority of cases tests on blood and synovial fluid were in agreement Occasionally the reaction was positive on blood serum, though not yet positive on synovial fluid When differences were noted, the blood serum, except in one case, gave a positive reaction before synovial fluid gave such a reaction Therefore, there is no advantage in testing synovial fluid rather than blood In three cases very early in the disease, gonococci were found in synovial fluid, but complement fixation tests on blood and synovial fluid were negative In three other cases it was possible to watch the tests change from negative to positive In cases in which both syphilis and gonorrhea were present a positive Wassermann reaction did not disturb complement fixation of gonococcal antigens

Tests were done on 71 controls 24 patients who had rheumatic fever, 30 who had atrophic arthritis, and 17 who had other articular diseases (tuberculous, hypertrophic or hemolytic streptococcic arthritis or Charcot's joints) A positive test was obtained from only two a 14 year old boy who had rheumatic fever, and a girl who had rheumatoid arthritis and psoriasis A doubtful test was obtained in a case of rheumatic fever accompanied by old, proved gonorrheal prostatitis

The investigators concluded that the routine use of the test on patients who have arthritis seems indicated and that a positive test is highly suggestive of the gonorrheal nature of an arthritis Tests should be repeated in all cases, especially when their results seem at variance with other data However, when the history and clinical findings suggest gonorrheal arthritis, but organisms cannot be isolated from synovial fluid or the genital tract, a positive test on blood or synovial fluid affords data of diagnostic worth

[These interesting studies need confirmation Such a test, if reliable, would be of much value The authors omitted certain desirable details They stated that a certain number of tests were positive "at some time in the course of the disease" More data should be given regarding the initial positivity of the test in relation to exposure to infection, and to the appearance of genital and articular disease Controls should include normal persons as well as patients who have various articular diseases—Ed]

Other tests on synovial fluid Cell count The total cell count on infected fluids varied between 7,350 and 158,000 per cubic millimeter, and on non-infected fluids from 1,800 to 78,250²⁰ Polymorphonuclear leukocytes formed 46 to 100 per cent of the cells Clasmatoocytes and monocytes were commonly present, in a ratio of 1 to 16 per cent and 1 to 33 per cent respectively Lymphocytes varied from 1 to 33 per cent, rarely was the percent-

age more than 10 In infected fluids the percentage of polymorphonuclear cells was always more than 76 Non-infected fluids generally contained more monocytes and clasmotocytes than infected fluids ²⁰

Chemical determinations The concentrations of total protein, non-protein nitrogen, and sugar in blood and synovial fluid were determined,²⁰ but the data were not of diagnostic value Estimations of total protein were of significance only as they, with the cell counts, indicated the presence of an exudate, not of a transudate According to Forkner (1930), since bacteria utilize sugar in their metabolism, a low concentration of sugar in synovial fluid in a case of arthritis suggests bacterial arthritis, and the lower the concentration of sugar the greater the likelihood of positive cultures being obtained from joint-fluid Myers and his colleagues ²⁰ found that the concentration of sugar in synovial fluid depended on three factors—the concentration of sugar in the blood, the synovial leukocyte count, and the presence of microorganisms in the fluid—but that of the three factors the first two were more important than the third Inasmuch as a low concentration of sugar was found in non-infected synovial fluids, a reduced concentration of sugar did not always indicate the presence of organisms Thus, Forkner's generalization was upheld, but only in part

Treatment Fever therapy Accumulating evidence indicates that fever therapy is the treatment par excellence for gonorrheal arthritis and that in the majority of cases not only are articular lesions markedly and promptly benefited thereby but also gonorrheal lesions elsewhere in the body In 12 cases of acute gonorrheal arthritis treated by Simpson ²² with radiotherapy or with heated, air-conditioned cabinets, results were uniformly successful and all patients became free of symptoms Jones ²³ expressed the opinion that fever therapy is practically specific in such cases All of his 10 patients who had acute gonorrheal arthritis, of three to 12 weeks' duration, were "cured" Joints became symptom-free and urethral discharges generally ceased after two to five treatments Hedrick ²⁴ also noted marked improvement in one acute case "Striking results" were obtained by Kovacs ^{25, 26} even in cases of stubborn chronic gonorrheal arthritis Doses of fever generally preferred are five hours at 105 to 106.5° F Two to six sessions of fever are generally given, one about every four days ^{22, 27}

Fever therapy is a highly specialized form of treatment The Council on Physical Therapy of the American Medical Association ²⁸ has recommended that the technic of its administration be given as much study as a surgeon gives his specialty It should be administered only by a trained personnel under the supervision of a physician familiar with the reactions Under such circumstances fever therapy is an essentially safe procedure However, The Council's report lists 29 deaths among 4809 patients who had various diseases which were treated by hyperpyrexia (a mortality of 0.6 per cent)

[Many of the deaths undoubtedly were of patients who had neurosyphilis, and some deaths should be ascribed to the disease, not to the treatment—Ed]

Other measures Where fever therapy is not available, older methods must be invoked The usual forms of therapy for gonorrheal arthritis were listed by Hedrick,²⁴ and include administration of stock and autogenous vaccines, intramuscular injection of autogenous synovial fluid, foreign protein therapy, administration of convalescent serum, injection of the prostate gland and seminal vesicles with various chemical substances, intravenous injection of meicrochrome, deep roentgen therapy, aspiration, and irrigation or open drainage of joints In addition to certain of these measures, Hedrick expressed himself in favor of intravenous injections of ammonium iodoxy benzoate, twice a week, four to 10 injections in all, aspiration or irrigation of joints and insufflation with air, and in refractory cases, fever therapy

[The wave of enthusiasm for ammonium iodoxy benzoate and allied substances in cases of atrophic arthritis has about run out—Ed]

Aspiration of large effusions generally gives considerable relief of pain²⁵ Particularly in cases of gonorrheal pyoarthrosis are aspiration and irrigation indicated²⁴ Irrigation with 1 to 5000 solution of mercuric chloride is a method for which Oxford²⁹ expressed favor Insufflation of air, as proposed by Porter and Rucker (1929) has the approval of some After aspiration, 75 to 100 c c of air³⁰ are injected, or enough to create a pressure of 40 mm of mercury²⁴ The air is absorbed in three to four days and insufflation can be repeated Presumably the air helps to prevent adhesions by keeping synovial folds apart It is suggested, also, that nitrogen mixed with the injected air may inhibit growth of gonococci Taylor³¹ approved injection through the rectal mucosa, into the prostate gland, of Pieg's iodine solution Excellent results not only for the genital infections but also for the arthritis have been claimed by him and by others

Prognosis and Results of Treatment In a given case, prognosis is difficult Some patients recover rapidly without permanent disability In many cases the disease results in progressive, chronic arthritis with restriction of motion or ankylosis Reinfection occasionally retards healing The poorest results seen by Myers, Keefer and Holmes²⁰ were in cases in which the cell count of the synovial fluid was more than 40,000 per cubic millimeter and the fluids were infected In such cases residual chronic arthritis often eventuated Those patients who recovered completely were as a rule those who had non-infected fluids, in which the leukocyte count was low, or infected fluids in which the leukocyte count was low Even so, the outlook for complete articular recovery was not good Only 37 per cent of the 69 patients recovered without signs of disease of joints

[These statements presumably refer to cases in which treatment was other than by fever therapy As we have noted, results therewith are very much better than with other forms of treatment, especially when the arthritis can be treated by fever therapy within the first two to four weeks of its onset—Ed]

TUBERCULOUS ARTHRITIS

The incidence of tuberculous arthritis is on the decline, partly because of certification of herds and pasteurization of milk. Tuberculous arthritis is always secondary to a tuberculous lesion elsewhere in the body. The infection is blood-borne to joints. Henderson^{32, 33} found that various joints were affected by tuberculous arthritis in the following order of frequency: spine, knee, hip, elbow, ankle, shoulder, wrist. Symptoms are stiffness, pain, local increase in temperature, swelling, deformity and, if the lower extremities are involved, limp. Children give "night crics," adults experience "night jerks," the latter are attributable to muscular relaxation, followed by sudden contraction in sleep. Tuberculous arthritis is persistently chronic although incomplete remissions occur. When it afflicts adults it is generally monarticular, although it may be polyarticular, it is more often polyarticular when it affects children than when it affects adults.

Of 274 proved cases of tuberculous arthritis of a knee seen by Henderson, in two-thirds the patients were males. Trauma was an inciting or precipitating factor in 13 per cent. Only 8 per cent of patients gave family histories of tuberculosis. In 44 per cent of cases tuberculosis was found elsewhere in the body. In 91 per cent articular bone was involved, in 9 per cent only synovia was affected. In 50 per cent bone abscesses were present, in 11 per cent, sequestra occurred.

Roentgenograms Henderson expressed agreement with his colleagues, Ghormley, Kirklin, and Brav,³⁴ that roentgenograms, although often characteristic, do not give incontrovertible evidence. Comparing the alterations in 65 cases in which the presence of tuberculous knee joints was proved, to those in 11 cases of non-tuberculous arthritis (gross and microscopic sections also being studied) Ghormley, Kirklin and Brav found them to be essentially similar. In very early tuberculosis, roentgenographic signs were absent. For a time, in the non-tuberculous case more change will be seen than in the tuberculous case. Marginal erosions, and long preservation of articular spaces were seen in both but were more suggestive of tuberculous involvement. Marginalipping, seen in both, was more often present in non-tuberculous cases. In tuberculous arthritis, areas of greatest destruction of cartilage or bone were either central or marginal, in non-tuberculous arthritis destruction was practically always central. Bone abscesses and sequestra indicate tuberculous arthritis, but in a large percentage of cases sequestra, when present, were not visible in roentgenograms. In one case of proved tuberculous arthritis of a knee associated with tuberculous spondylitis, seen by Bennet and Hinricson,³⁵ the roentgenographic appearance resembled that of a Charcot joint, and the latter diagnosis was entertained for a time particularly as the knee was painless.

Pathology Herniation of joint cartilage into subchondral tissue and plication (folds or pleats) were frequently noted by Freund³⁶ in tuberculous joints, in which undermining of joint cartilage is extensive. It does not

lead to marked deformity of the surface of the joint because the entire cartilage usually becomes resorbed or sequestered

Synovial Fluid The total cell counts of synovial fluid in five cases were found, by Keefer, Myers and Holmes,¹¹ to vary between 6,500 and 110,000 per cubic millimeter. The differential count was as follows: polymorphonuclears 45 to 93 per cent, lymphocytes 3 to 30 per cent, monocytes 1 to 31 per cent, clasmatocytes 1 to 7 per cent, eosinophiles 0 to 3 per cent. The differential formula thus disclosed no absolutely characteristic features, but there were generally more lymphocytes and monocytes than in other types of arthritis. Chemical examinations revealed no characteristic alteration: total protein per 100 c.c. of synovial fluid varied between 4.3 and 5.5 grams, the non-protein nitrogen of fluid equalled that of blood, the sugar of the fluid (91 to 160 mg.) was always a few milligrams higher than that of the blood (79 to 116 mg.)

[The sugar determinations on synovial fluid did not always represent fasting values—Ed.]

Treatment Henderson expressed the opinion that non-operative therapy is erroneously called conservative treatment. In fact surgical treatment, arthrodesis (at least if patients are more than nine years of age), may be more conservative, and more saving of time and money, even though it is granted that a few patients can be cured by long rest and articular fixation under supervision in hospitals. The knees, hips, shoulders, and spine are best suited for arthrodesis, the elbows, wrists, and ankles are next in choice. Of 274 cases of tuberculous arthritis of the knees, in which Henderson^{32, 33} performed arthrodesis between 1913 and 1934, fusion resulted in about 90 per cent. Nine per cent of the patients were found to have died of their non-articular tuberculosis. Synovectomy was performed on four patients whose articular tuberculosis was confined to synovia. Of these four patients two were well and comfortable several years later.

“TUBERCULOUS RHEUMATISM”

An extensive résumé of literature on this subject has been made by Brav and Hench.³⁷ As described by its proponents, this condition is a form of polyarthritis, simulating in some cases acute rheumatic fever, in other cases, chronic atrophic arthritis, but bearing some etiologic relationship to tuberculosis. It is thought to be attributable to a tuberculous toxin from some distant focus, a filtrable virus, an attenuated form of the bacilli of tuberculosis, or an allergic reaction. True tubercles are not the expected finding, and when present, they indicate superimposed tuberculous arthritis rather than tuberculous rheumatism. Evidence for the diagnosis of tuberculous rheumatism includes familial tuberculosis, associated visceral tuberculosis, demonstration of Koch's bacilli in synovial fluid and the blood stream, positive results of inoculation of guinea pigs with joint-fluid, and in some cases the presence of a typical tuberculous joint before, coincident

with, or subsequent to, the development of polyarthritis. Reported pathologic findings have included focal collections of round cells, of plasma cells and of histiocytes, isolated instances of necrosis, internal thickening and vacuolization of the vessels, and the presence of giant cells and endothelial cells. These alterations are considered either a transition stage between simple inflammatory tissue and tuberculosis, or an allelic manifestation of the latter.

Against acceptance of the syndrome of tuberculous rheumatism have been arrayed a large number of competent investigators who argue that there is no adequate clinical method of identifying it, no consistently characteristic roentgenographic evidence, no experimental or laboratory evidence in its favor that is not highly controversial, and no consistent demonstration of its supposedly characteristic microscopic pathology.

A statistical study by Brav and Hench of a series of 150 cases of acute rheumatic fever and 250 cases of chronic atrophic polyarthritis revealed no significantly higher incidence of familial tuberculosis or associated visceral tuberculosis than that found among 250 control cases. The controls were consecutive non-arthritic cases, studied in the same period as the arthritic series. The control patients registered a multiplicity of complaints in no way related to joints. Of a series of 75 cases in which a diagnosis of chronic atrophic polyarthritis had been made, and in which the pathologic characteristics of a single joint were determined by microscopic examination of tissues or by inoculation of guinea pigs, the joints of eight patients were found to be definitely tuberculous. In each of the eight cases, the tuberculous nature of the arthritis was suspected prior to examination of tissue or inoculation of animals, but the presence of polyarthritis was confusing. Brav and Hench concluded that further investigation will be required to determine the acceptance or rejection of the syndrome of tuberculous rheumatism. At present, they concluded that no incontrovertible proof of such an entity exists.

LeSage,³⁸ however, accepting the entity without question, was surprised how seldom the condition was diagnosed and how often it was confused with gonorrheal or gouty arthritis. He admitted that generally no direct proof of its tuberculous nature can be found either on pathologic or bacteriologic examinations. "We have only clinical signs to guide us," he wrote. In a few cases, although cultures and examination of the joints may be negative, the subcutaneous or intraperitoneal inoculation of bacteriologically-negative synovial fluid into guinea pigs will produce tuberculosis. LeSage expressed the belief that a tuberculous virus may manifest its presence in serous membranes only by ordinary, simple, inflammatory lesions in the "pre-bacillary stage." In the later "bacillary stage" the primary inflammatory lesions undergo evolution to the state wherein their tuberculous nature may be revealed.

In evidence, LeSage included the following cases. A man, aged 26 years, in 1923 had vague pains and stiffness in the neck and spine, inflammation and ankylosis of the right ankle. The case progressed as follows: in 1924, involvement of the left ankle, in 1925, of the temporomandibular joint, with orbital neuritis, in 1926, progressing "rhizomorphous spondylitis", in 1930, swelling of the left knee, in 1931, left orbital neuritis, corneal ulcerations and amaurosis, in 1932, involvement of the right knee, and in 1933, involvement of both shoulders. Roentgenograms disclosed the following: those of the thorax "ganglionic spots with dense peribronchial and pulmonary fibrosis", those of the joints, destructive arthritis, exostosis and rarefaction. Fluid removed from the right knee in 1932, when injected into guinea pigs, produced extensive tuberculosis, and bacilli were recovered.

A woman, aged 61 years, had arthralgia of the feet and effusion of the left knee. She presented no evidence of tuberculosis. The cutaneous reaction was positive for tuberculosis. Fluid from the knee joint was negative, as was the guinea pig test, but culture of the patient's blood (Lowenstein's technic) gave colonies of virulent Koch's bacilli after three weeks.

From such evidence, LeSage concluded that lesions of inflammatory tuberculosis (ante-bacillary period) are attributable to a filtrable virus, whereas specific lesions are produced by Koch's bacillus.

[In three other cases the diagnosis seems to have been made chiefly from clinical data, data which may have been clinically unmistakable to LeSage, but perhaps inadequate for others—Ed.]

To Buckley³⁹ much of the evidence for the entity was unconvincing. Positive cutaneous reactions may easily be attributable to latent tuberculous foci in lymph nodes or elsewhere, and isolation of bacilli of tuberculosis from the blood in cases of acute polyarthritis, by the method of Reitter and Lowenstein (1932), generally has been unsuccessful in other hands. In two cases of chronic polyarthritis, Buckley found bacilli of tuberculosis in effusions from knee-joints. Admitting the possibility that a chronic tuberculous focus in lymph nodes, or elsewhere, may sensitize tissues to, and thus favor infection by, streptococci, it seemed more probable to Buckley that sensitization is first produced by streptococci and that infection by bacilli of tuberculosis occasionally follows.

PNEUMOCOCCAL ARTHRITIS

This rare disease occurs only once in every 800 to 1000 cases of pneumonia. When pneumococci gain access to a joint they produce acute, generally purulent, arthritis. Fagge⁴⁰ reviewed the literature, and the experience of the physicians of Guy's Hospital between 1918 and 1932, during which years only seven cases, including at least two that were doubtful, were seen. Three-fourths of cases of pneumococcal arthritis occur in conjunction with pulmonary infection, generally after the stage of resolution, occasionally in the stage of red hepatization. A fourth of the cases occurs in association with pneumococcic septicemia but without pneumonia. Larger joints are generally involved, the knees most commonly, next in frequency of involvement are the shoulders, wrists and elbows. In three-fourths of

cases the involvement is monarticular. When pneumonia is present the appearance of acute arthritis raises the suspicion of its pneumococcic origin. Otherwise the diagnosis is made on bacteriologic examination of aspirated joint-fluid. In spite of purulent exudates and gross involvement, complete articular restitution often occurs and ankylosis is rare. Of patients so affected, 24 per cent die from non-articular pneumococcic infection.

Of Fagge's patients, one had pneumococcic meningitis, and a shoulder was affected, one had pneumonia and a knee was involved, one acquired influenza shortly after spraining an ankle, and pneumococcic abscesses developed about the affected ankle. In the cases at Guy's Hospital, pneumococcus type I was found once, type III, twice.

Farah⁴¹ described a different course of presumed pneumococcic arthritis in one case.

A man, aged 31 years, acquired a sore throat and bronchitis in 1924. Fifty days later subacute, febrile monoarthritis of the right knee developed and was evident for a few days. Complete restitution occurred. In July 1924, without any associated sore throat, the left knee became similarly involved and remained involved for 20 days but recovery was complete. In December 1925, three days after onset of a sore throat, the right knee and left wrist were briefly affected, in February 1927 the patient again had a sore throat and an involved right knee. In the next six years he had repeated mild attacks in one to three joints, occasionally after onset of a sore throat or cold. These and all previous attacks apparently responded notably to salicylates. In February 1933, generalized febrile polyarthritis developed. Roentgenograms of joints were normal in spite of repeated involvement through 10 years. The heart was normal. From the blood pneumococci were obtained in pure culture. From the red throat, pneumococci, type III were obtained and agglutinins thereof were present in the serum in a titer of 1 to 2000. Skin tests to several bacteria were negative but to the pneumococci obtained from the patient were strongly positive. Articular cultures were not permitted.

Farah assumed the case to be one of an unusual form of pneumococcic arthritis from focal infection (pneumococcic sore throat), of special interest because of the absence of purulent effusion or articular residues, and because of the later resemblance to acute rheumatic fever, including response to salicylates. He suggested that other cases of acute rheumatism may be so caused.

[It is to be noted that the early attacks were monarticular, not typical of rheumatic fever. Somewhat similar cases of recurrent monoarthritis and polyarthritis of short duration, leaving no residue in joints or heart, have been reported as instances of allergic arthritis. This report should stimulate appropriate investigations in unclassifiable cases. One of us saw a case in which a parotitis was the only infected focus. Pneumococci could always be isolated from saliva but not from joints.—Ed.]

Pathology Details of pathologic reactions in a case of pneumococcic arthritis of an elbow joint were described by Keefer, Parker and Myers.¹⁵ An intense inflammatory reaction of synovia—thickening of subsynovial fibrous tissue and destruction of synovial surface cells—and extensive destruction of cartilage and subchondral bone were noted.

Treatment Immobilization, prompt articular aspiration and irrigation with physiologic saline solution, repeated as necessary, are advocated^{15, 30}

SCARLATINAL ARTHRITIS, POSTSCARLATINAL RHEUMATISM

In the course of, or following, scarlet fever the joints or heart may be affected in about 6 to 10 per cent of cases by (1) toxic lesions appearing early in the disease, (2) septicopyemic lesions appearing early or late, and (3) so-called allergic lesions which generally appear late. Both the suppurative and the non-suppurative varieties of scarlatinal arthritis, or post-scarlatinal rheumatism, have been considered by some to be more or less specific manifestations or complications of scarlet fever. Others believe that the non-suppurative forms, with or without carditis and with or without a previous history of rheumatic fever, should be regarded as forms of true rheumatic fever, activated by the hemolytic streptococcal infections of scarlet fever in the same way that other streptococcal infections are prone to activate latent rheumatic fever. Comparing epidemiologic studies in cases of postscarlatinal rheumatism with those in cases of rheumatic fever, Paul, Salinger and Zuger⁴² expressed agreement with the latter viewpoint. A high incidence of rheumatic fever was found in families of patients who had had postscarlatinal non-suppurative arthritis or carditis. The clinical course of these two complications is essentially similar to that of rheumatic fever. Although every case of non-suppurative arthritis or carditis following scarlet fever is not necessarily a manifestation of rheumatic fever, the majority probably are, and are not specific complications of scarlet fever.

The case of a boy 14 years of age who suffered from fever and a red, swollen hip a few days after inoculation against scarlet-fever was reported by Stewart⁴³. In the next five months, while the patient remained in bed destructive arthritis and marked stiffness of the hip appeared. Since, in roentgenograms, the epiphyseal line seemed open and motion of 10° was present, motion was encouraged. Finally flexion of 40°, hyperextension of 10°, and rotation of 30° were accomplished by the patient. At last he could sit in a chair and walk a mile and a half without pain. Fluoroscopy gave evidence of pseudo-arthrosis, motion originating wholly in the epiphyseal line.

[Bacteriologic studies relative to the hip apparently were not made, and the data furnished do not permit a positive diagnosis—Ed.]

SYPHILIS AFFECTING JOINTS

Clutton's Joints, Symmetrical Serous Synovitis The most common articular affection of congenital syphilis among children is Clutton's joint, a relatively painless, simple, serous or gummatous synovitis which is generally bilateral, lasts for months or years, and is not accompanied by bony changes. It generally affects one or both knees, one being affected some

time before the other. Elbows, wrists or fingers are less frequently affected. It is uncommon among adults who have acquired syphilis. When present it usually precedes or accompanies the secondary eruption. Of 363 cases of congenital syphilis encountered by Klauder and Robertson,⁴⁴ in 63 Clutton's joints were present, one or both knees were involved in all, and in two an elbow also was affected. Little or no pain, tenderness, heat, redness, limitation of motion, or muscular atrophy were present. The patients were generally from eight to 15 years of age. Pathologic reactions include formation of villous processes and synovial fringes and simple or gummatous synovitis. Untreated, the process becomes chronic but generally terminates spontaneously. Antisyphilitic therapy may affect it markedly or not at all. Splints, rest and surgical operation seem useless. In all of Klauder and Robertson's cases effusions eventually disappeared without ankylosis. If ankylosis is present the condition is not Clutton's joint but may be syphilitic arthritis. Patients who have Clutton's joints are more likely than others to suffer from interstitial keratitis.

Eleven cases of chronic synovitis of the knees, with persistent or recurrent effusions, were seen among children by Gill and Orr⁴⁵ and were considered very similar to cases of Clutton's joint although Wassermann reactions on blood and spinal fluid were negative in all but two. In one of the latter a positive reaction was obtained only after administration of provocative doses of neoarsphenamine. Tissue obtained in one case revealed a red, thick synovial membrane, synovial fringes and early formation of pannus, with some erosion of underlying cartilage.

[Gummatous infiltrations were not mentioned—Ed.]

Although the etiology was undetermined, all the cases were thought possibly to be syphilitic. In similar cases Klauder and Robertson recommended provocative tests. Only one case was cured by therapy. Buck's extension, casts, splints, braces, physiotherapy, heliotherapy, compression bandages, repeated aspirations.

[Antisyphilitic therapy apparently was not administered. It seems to us that one has no right to make or suggest a diagnosis of Clutton's joint in a patient with negative Wassermann reactions on blood and spinal fluid unless the parents reveal evidences of syphilis, or the patient shows stigmata of congenital syphilis. Some believe that conservative treatment of Clutton's joints is generally followed by recovery whether or not specific antisyphilitic treatment is administered—Ed.]

Syphilitic Arthritis The Wassermann reaction was performed by Keefer, Myers and Holmes¹¹ on four specimens of synovial fluid from two patients who had syphilitic arthritis. The blood serum and synovial fluid were positive on three occasions, once the reaction of blood serum was positive when that of synovial fluid was doubtful. In two cases the cytology of the synovial fluid was as follows: total cells per cubic millimeter 3,200 to 4,500, polymorphonuclears 17 to 52 per cent, lymphocytes 35 to 51 per cent, monocytes 7 to 32 per cent, clasmotocytes 3 to 16 per cent. In one

case the total concentration of protein in the synovial fluid was 3.8 gm per 100 c c , of sugar, 78 mg , of non-protein nitrogen, 24 mg

UNDULANT FEVER

The symptomatology of this disease was reviewed by Miller⁴⁶ An almost constant symptom is arthralgia, sometimes severe enough to suggest acute arthritis In some cases articular pain and tenderness are present, but no swelling Some cases resemble instances of acute rheumatic fever If the patient has an afebrile period, the joint disturbance may largely subside In one of Miller's seven cases, the spindle-shaped swellings of the fingers resembled those seen in atrophic arthritis, and in this case the diagnosis of atrophic arthritis had been made An intermission in the fever was followed by disappearance of the swellings Suppurative arthritis of costosternal or costochondral junctions, and suppurative spondylitis, have been reported by others Blood cultures, when positive, as they are in only 25 per cent of cases, establish the diagnosis Agglutination tests are useful but variably positive, in many active cases they are negative unless repeated frequently

A case of undulant fever, resembling a case of acute rheumatic fever, was seen by Twedell and Schlotzhauer⁴⁷ A young man had sore throat, malaise, pains in the chest and right knee, and later had headache, cough and fever In a few days the pain in the knee disappeared but migratory pains affected the opposite leg, shoulders, and elbows A diagnosis of rheumatic fever was made but the effect of salicylates was poor A month later an enlarged spleen was noted Several blood cultures revealed *Brucella abortus* and agglutinins were present in a titer of 1 to 1,600

Treatment According to Miller, treatment with specific vaccines and chemotherapy is not of proved value Occasional results from typhoid vaccine or arsphenamine are reported In a case of three months' duration, seen by Jones,²⁸ one session of fever therapy (two and a half hours at 105.5° F) was followed in a few days by complete cessation of malaise, weakness and fever

[Arthritis was not mentioned as being present in this case—Ed]

Experimental Undulant Fever Feldman and Olson⁴⁸ were unable to produce demonstrable lesions in swine by injection, by various routes, of strains of *Brucella abortus* of porcine origin, consistently pathogenic to guinea pigs Agglutinins were produced in the blood serum of all animals that received injections Although the strains had been isolated from lesions of spontaneous spondylitis of hogs, no similar lesions could be reproduced experimentally It is concluded that the apparent predilection of such organisms for vertebral bodies does not represent an inherent tendency of the organism for elective localization, but that the predilection is accidental or casual

HAVERHILL FEVER, ERYTHEMA ARTHRITICUM EPIDEMICUM

Full details of this disease, one of recent identification (Levaditi, Nicolau, Poincloux, Place, Sutton, Willner, 1926) were given in three reports. Haverhill fever has four main characteristics: (1) an abrupt onset with chills, fever, malaise, vomiting and headache, (2) an early eruption, rubelliform or morbilliform, occasionally first, and often only, on the extremities, especially about the ankles and wrists, with a tendency to become hemorrhagic, (3) multiple arthritis of varying, but often of severe, degree and (4) a peculiar remittent (saddleback) fever curve, of abrupt rise, with remission in from two to five days, and after a few days of relative freedom from symptoms a febrile recurrence with which the arthritic manifestations appear.⁴⁹

Symptoms referable to joints are outstanding and distressing. Generally they appear with the secondary rise of fever, on the third to the fifth day of the disease, very occasionally later. Several joints may be attacked, the wrists, elbows, knees, shoulders, fingers and ankles most commonly. Joints may be markedly painful, redness and swelling are variably present. Roentgenograms of joints are negative. Muscles are "lame" but not tender. Hydrops is often present in a knee, and in two cases pure cultures of the causal organism, *Haverhillia multiformis*, have been isolated therefrom.^{49,50} The arthritic symptoms may last from a few days to several months, but generally they last about four weeks. They may persist longer than the fever. In general, articular restitution is complete or almost so.

The condition must be distinguished from rheumatic fever, which has no such peculiar fever curve, from dengue, from infectious erythema with arthralgia, from erythema multiforme, from Malta fever, and from rat-bite fever. In Haverhill fever the heart is negative, and although sore throat is a common symptom it is a diffuse catarrhal type of injection without exudate or tendency to involve lymphoid tissue, such as is seen in rheumatic fever. The diagnosis is confirmed by isolation of the specific organisms from the blood or from joint fluid. Specific agglutinins are present. Unpasteurized milk is believed to be the usual source of infection, but Scharles and Seastone⁵¹ have shown that the condition may follow a rat bite. A medical student who was bitten by a laboratory rat acquired the disease, and it was identified by agglutination tests and by recovery, by Bauer, in fluid from an ankle, of the specific organism of Haverhill fever. All attempts to find spirilla of rat-bite fever failed. It is suggested that certain cases of supposed rat-bite fever may in fact be cases of Haverhill fever.

SEPTIC (PURULENT) ARTHRITIS

The common forms of septic arthritis, aside from the gonococcal form, are attributable to *Staphylococcus aureus* or to *Streptococcus hemolyticus*. A hip, a knee, or a shoulder is most commonly affected, and roentgenograms often disclose no abnormality for the first 10 days.⁵² Early diagnostic

aspiration is recommended. Particularly if leukocytes number more than 15,000 per cubic millimeter of blood, and if thick pus is present, Oxford has expressed himself as in favor of arthrotomy with open drainage. Such treatment was necessary in 15 (60 per cent) of his 26 cases, in the remainder conservative therapy was permitted such as drainage by aspiration and then traction or fixation. Ankylosis, however, frequently results, particularly if the arthritis arose from infection (osteomyelitis) of juxta-articular bone. The most marked alterations in synovial cytology, noted by Keefer, Myers and Holmes,¹¹ were seen in three cases of arthritis caused by hemolytic streptococci. The total number of cells per cubic millimeter varied from 109,500 to 350,000, and polymorphonuclear cells constituted 94 to 100 per cent thereof.

The articular pathology in two cases was described by Keefer, Parker and Myers¹⁵ and included synovial thickening and cellular infiltration, with regions of complete destruction, cartilaginous thinning and erosion, infiltration of leukocytes, abscesses in bone marrow, and masses of visible bacteria.

In four cases in which treatment was administered by Taylor,⁵³ transfusions were employed and bacteriophage seemed of value.

ARTHRITIS OF SUBACUTE BACTERIAL ENDOCARDITIS

Pains of the joints commonly occur with infective endocarditis. The joints do not suppurate. Their pathology has not been described heretofore. In a case of subacute bacterial endocarditis affecting a young man, and attributable to an unidentified form of gram-negative coccus, Keefer, Parker and Myers¹⁵ found the essential articular lesion in the synovial connective tissue with perivascular lymphocytic infiltration. The synovial surface cells were generally intact.

MENINGOCOCCIC ARTHRITIS

Brief clinical details of two cases, with pathologic reactions found at necropsy, were reported by Keefer, Parker and Myers¹⁵. Arthritis occurs in from 4 to 7 per cent of cases of meningococcic meningitis (Herrick and Parkhurst, 1919) and may assume three forms. 1 One form comprises brief, early polyarthritis characterized by pain and tenderness but without swelling or hydrops, and generally accompanied by a hemorrhagic rash. The joint pains may be attributable to hemorrhages in articular and peri-articular tissues. 2 Metastatic pyoarthrosis with meningococci in the effusions is characteristic of the second form. Recovery occurs in one to four weeks, with or without ankylosis. 3 Arthralgia from meningococcus serum constitutes the third form. From their studies, the writers¹⁵ concluded that in meningococcic arthritis the metastatic lesion involves deeper synovial tissues first, later, the superficial cells, with effusion of fluid into the joint cavity and varying degrees of destruction of cartilage.

In a case in which chills, fever, jaundice, meningitis and meningococcic arthritis developed, and which was seen by Jaffe,⁵⁴ the use of meningococcus serum was followed by relief of all symptoms and signs, but the patient later died of pneumonia

RHEUMATIC FEVER

Incidence Some studies indicate that the incidence of rheumatic fever depends largely on various factors of climate and environment the patient's geographic habitat, his social condition, exposure to damp, cold and respiratory infections, and to seasonal change Glover and others⁵⁵ have reminded us that the Medical Research Council's investigation, which included familial incidence and heredity, familial evidence of sore throats, maternal care, exposure, sleeping conditions, clothing, birthplace, occupation, income of parents, types and sites of houses, and so forth, concluded with the statement that the findings were largely negative It is nevertheless felt by many that some of these factors are important, and Glover and Miller and others^{55, 56} have voiced the general belief that the incidence of rheumatic fever and rheumatic heart disease is low in the tropics, higher in the temperate zone and among persons living near sea level or in basements, and also that it is higher in cold, damp months

Geography Reviewing the distribution of rheumatic heart disease, which is the best proof of the existence of rheumatic fever, in various parts of the world, Nichol⁵⁷ reported that it is prevalent and severe between latitudes 50° and 40° North, diminishes in warmer climates, is almost unknown between the Tropics of Cancer and Capricorn, increases again as cooler climates are reached and is common between latitudes 30° and 40° South Thus it is practically unknown in the subarctics, in southern India, Puerto Rico, southern China, the Malay States and Panama It is common among school children in England (1.5 to 2.0 per cent), northern Europe, northern United States of America (0.89 to 0.66 per cent), South Africa and Australia Its incidence varies widely in the United States, from 0.86 in Boston to 0.45 per cent in Miami Admissions to hospitals are more impressive, for a variation of 0.2 to 5.8 per cent exists, the latter in cold wet climates, and the former in warmer regions Rheumatic fever and chorea are rare in Florida, according to Nichol (16 cases in 16,200 medical admissions to hospitals) Rheumatic heart disease is particularly rare among children born in Miami and is seen three times as often among children now living in Miami but born in the North Of 103 patients who had rheumatic heart disease, seen in a given period, in only seven cases did it originate in southern Florida Simmons⁵⁸ found the incidence of rheumatic heart disease in Kentucky to be the same as that in Texas and Louisiana, half that of Virginia and Maryland, and a fourth that of New England According to Chase⁵⁹ it is rare in Oklahoma, a warm, dry state, it is becoming less frequent in Omaha, Nebraska,⁶⁰ and although it is increasing in the United States as a whole it is not increasing in New York City⁶¹

Compared to its incidence in Great Britain, rheumatic heart disease is relatively infrequent in Australia Cleland⁶² found 116 cases (3.9 per cent) in 3000 postmortem examinations

[Figures are not given to support some of these later statements—Ed.]

Social Conditions It is believed that the disease is more common in crowded cities than in the country, and that poor hygiene and environment favor its development In Australia it is more common in the city and suburbs (194 of 218 cases came from the city and suburbs) than in the country, but it is common in the hill districts and low-lying valleys⁶³ Although poverty is a factor, children of the poorest parents are less affected than those of less poor parents (Miller) Glover expressed the opinion that the true incidence of the disease is directly proportional to the degree of poverty, and that it is seen 20 to 30 times more frequently among children of the poor than among those of the well-to-do The incidence of rheumatic heart disease was 48 per 1000 children in a public school in the poorest city district, 31 per 1000 children in public school in a better residential area Thus, the former was one and five-tenths times higher than the latter, but it was moreover found to be eight times higher than the incidence among children of a wealthier class from urban private schools From these figures, Paul, Harrison, and DeForest⁶⁴ concluded, again, that rheumatic heart disease is in part a manifestation of poverty

Effect of Seasons In England, rheumatic fever is more prevalent in the cold, damp months of fall and winter,⁶⁵ but in Rochester, New York, it is more common in late winter and spring⁶⁶

Heredity A high family incidence is frequently reported, Swift⁶⁶ recently indicated that he still believed this phenomenon means an inherited state Thus a hereditary tendency is present in a third of the cases, according to Benjamin,⁶⁷ who found that of 280 rheumatic children, 38 per cent had rheumatic parents and 17 per cent had rheumatic brothers or sisters

Physical Type Although the rheumatic child may differ from the normal one in other constitutional traits, he does not differ in physical type, as indicated by bodily dimensions, sexual differences, color of hair and eyes, type of contour (slender or thick) or posture, according to the exhaustive report of Young⁶⁸ who studied 1,212 children, 459 of whom were rheumatic, 368 asthmatic, and 385 normal

Sex and Age Juvenile rheumatism is more frequent among females^{65, 67} Of Kaiser's 1200 rheumatic children, 54 per cent were girls, 46 per cent, boys Kaiser noted the disease infrequently among patients who were less than the age of three years, he found an increasing frequency among patients from three to 10 years of age, and a declining frequency among those from 10 to 15 years of age, thereafter the condition was as infrequent as it was before the age of three years Only six cases of rheumatic heart disease of children less than two years of age have been reported White (1926) saw a patient who was sixteen and a half months old, and

Schroeder (1922), one 20 months old As Swift⁶⁶ noted, the cases of rheumatic fever in very young infants have almost all occurred in instances wherein the mother had the disease while the child was in utero, this suggests that both the susceptibility, and the infectious agent were transferred to the infant during pregnancy because, in general, other infants of rheumatic families do not give clinical evidence of the disease until after the fourth or fifth year of life It is likely that during a considerable portion of this pre-rheumatic period the infant's tissues become so conditioned that they finally develop the capacity for showing true rheumatic lesions

The youngest patient on record has been reported by Fischer⁶⁹, the child was twelve and a half months old and died of rheumatic heart disease The mother had active rheumatic fever from the third to the seventh month of pregnancy The child developed fever, convulsions, otitis media, pneumonia and the typical picture of rheumatic valvulitis Aschoff bodies were found at the necropsy Fischer expressed the belief that the process was acute and probably did not date from birth although the child might have been stigmatized during fetal life

Symptoms The progress of the disease, as shown in new studies, conforms to the accepted pattern, major manifestations are sore throat, tonsillitis or infection of the upper part of the respiratory tract, fever, abdominal pains, arthritis, myositis, nodules, cutaneous eruptions, purpura, and carditis Of 206 patients who had rheumatic heart disease, seen by Simmons,⁶⁸ 68 per cent gave definite histories of rheumatic fever, 19 per cent had had only recurrent tonsillitis, 4 per cent gave histories of chorea and 8 per cent had none of these The first rheumatic attack occurred before the age of 20 years in 70 per cent of cases, before 30 years in 94 per cent In nine cases symptoms did not develop until after the age of 50 years As is well-known, and as has been emphasized again by Black,⁷⁰ the symptoms of the disease differ somewhat as they are seen in children and in adults The latter generally present an acute onset, high fever, polyarthritis and drenching sweats In children the symptoms are less definite slow onset, frequently infection of the upper part of the respiratory tract, malaise, growing pains, fatigue, intermittent fever, rapid pulse without fever, night sweats, pallor, anemia, epistaxis, chorea, occasional nodules and frequently slight cardiac murmurs Growing pains or chorea may be the only symptom⁶⁷ Nodules, generally over knuckles, occur in 15 to 20 per cent of cases^{67, 70} According to Benjamin⁶⁷ rheumatic growing pains are characteristic vague, dragging, fleeting pains in muscles, occasionally in joints, frequently accompanied by easy fatigability, loss of weight and anorexia

[According to Shapiro (1935) rheumatic growing pains are more often in joints, nonrheumatic growing pains of children are more often in muscles—Ed]

Some of the 1200 children seen by Kaiser⁶⁵ had six or more symptoms, others, only a few Pancarditis and nodules usually denote a serious form, tonsillitis, pallor and anorexia may indicate less serious rheumatism Major

manifestations were present as follows pericarditis in 64 per cent of cases, rheumatic fever with severe arthritis in 39 per cent, mild arthritis in 32 per cent, chorea in 29 per cent, muscular rheumatism (growing pains) in 18 per cent, pneumonitis in 3 per cent, erythema nodosum in 2 per cent, nodules in 1 per cent, pleurisy in 1 per cent and purpura in 0.4 per cent. Minor manifestations were present as follows tonsillitis or sore throat in 43 per cent, fatigue in 36 per cent, anorexia in 34 per cent, pallor in 30 per cent, epistaxis in 15 per cent, cephalalgia in 6 per cent, abdominal pain in 5 per cent, cardiodynia in 4 per cent and nausea in 3 per cent. Chorea was not as frequently associated with carditis as was arthritis. Those patients who had mild arthritis or myositis had less carditis than those who had acute fever or severe arthritis. Tonsillitis or pharyngitis immediately preceded arthritis, chorea or endocarditis in 43 per cent of cases.

According to some⁵⁸ the disease, in general, behaves similarly in all latitudes, producing the same cardiovascular and other lesions. According to Schlesinger⁷¹ the geographic variations are enormous, there is less carditis in the Netherlands than in England, more nodules in England than in America.

[In our last year's review, differences of opinion were noted as to whether the manifestations of the disease, when it occurs in the southern American states, are the same as those when it occurs in the north. The weight of evidence is in favor of geographic differences in symptoms. In the south the disease is milder, there is less arthritis for which reason the disease often goes undiagnosed.—Ed.]

Special Symptoms, Lesions, and Complications, with Pathologic Studies of Heart. Recent data confirm accepted ideas. Of Simmons'⁵⁸ 206 cases the mitral valve was involved alone in 83 per cent, the mitral with the aortic valve in 11 per cent, the aortic valve alone in 6 per cent. According to Cleland's⁶² report on rheumatic carditis in 88 cases, it was found that mitral stenosis was more common in females than in males, aortic valvulitis more common in men. Evidence of unsuspected rheumatic carditis is often found at death in the bodies of persons who presumably were clinically unaffected by the disease. Of all patients dying at the Presbyterian Hospital, New York City, aside from those known to have had rheumatic fever, 12 per cent were found, by Hawking,⁷² to have latent or active rheumatic carditis. The specificity of Aschoff bodies is doubted by some. Gross and Ehrlich⁷³ have made a contribution to the descriptive classification, life cycle, sites of predilection, and relation of the Aschoff body to the clinical course of the disease. They concluded that the myocardial Aschoff body is of a type specific for the myocardium and to be considered apart from other rheumatic lesions. Aschoff bodies pass through three stages. The earliest stage occurs up to the fourth week of the disease and presents small-cell coronal, and reticular, Aschoff bodies. The second phase occurs from the fourth to the thirteenth week and presents large-cell coronal, syncytial coronal, mosaic, and large irregular-cell polarized bodies. Polarized bodies occur

from the ninth to the sixteenth week, fibrillar bodies, after the thirteenth week. Aschoff bodies are found in 90 per cent of hearts of patients who die with evidence of active disease, in 59 per cent of those who die with evidence of old or recent activity.

It is generally believed that heart failure depends on myocardial rather than on endocardial damage, since degrees of the latter are not related to the occurrence or extent of cardiac failure. A study by Rothschild, Kugel and Gross⁷⁴ indicates that the severity of endocarditis bears no relation to the degree or age at onset of myocarditis and that rheumatic heart failure is related less to valvulitis, more to continued or recurrent myocarditis.

Blood vessels. Lesions in coronary arteries in rheumatic fever were described as being found in 56 cases by Karsner and Bayless,⁷⁵ and in four cases by Fraser.⁷⁶ In both articles specific lesions were described in detail, Karsner and Bayless also described vascular lesions not specific for the disease. There is a significant association between rheumatic heart disease and periarteritis nodosa (necrotizing arteritis) according to Friedberg and Gross⁷⁷ who reported four cases. An unusual case of portal obstruction, retroperitoneal varix and fatal hemoperitoneum, in the presence of rheumatic carditis and adherent pericardium, was seen by Feldman and Gross.⁷⁸ Easby⁷⁹ reported the appearance of spontaneous subarachnoid hemorrhage, possibly from a mycotic aneurysm, in a rheumatic child.

[The patient recovered, no pathologic data were given—Ed.]

Renal lesions. Opinions differ as to the incidence of renal lesions in association with rheumatic fever. According to Blaisdell⁸⁰ a high percentage of rheumatic patients suffer from renal damage early in life. Of 2400 consecutive cases which came to necropsy, in 128 active or healed cardiac lesions were found. Of the latter group 38 subjects exhibited interstitial nephritis, half had been less than 40 years of age at death, a third, less than 30 years. The reported pathologic details in 16 such cases were related to small vascular structures, cortical arterioles and intralobular and arcuate arteries.

Pulmonary lesions. The pulmonary complications of rheumatic fever, according to Klein⁸¹ include fibrinous pleurisy, pleurisy with effusion, atelectasis secondary to enlarged heart with pericardial effusion, vascular lesions of the pulmonary artery and its branches, and rheumatic pneumonitis. Symptoms of the latter may be evanescent, its course very variable, its characteristics hemorrhage and fibrinous exudate.

Cutaneous lesions, nodules and purpura. Nodules may be subcutaneous or cutaneous. Rosenberg⁸² has reviewed their clinical differences and the histology of the latter, they vary from the size of a pinhead to that of a hazelnut, last for variable periods, and appear most commonly on the fingers, palms, and neck, also on the forehead, chest, and cheeks. In an epidemic in a hospital, observed by Chester and Schwartz⁸³ the predominant sign was crops of bluish, not tender, maculopapular, purpuric spots, chiefly on

the legs and arms, lasting one to six months and disappearing without scarring or desquamation Holtz and Friedman⁸⁴ described an "unreported lesion" a hemorrhagic eruption confined to the mucosa of mouth and throat, seen rarely in examination of normal or nonrheumatic persons (occasionally in association with malnutrition, diabetes mellitus, vascular nephritis, and mumps), but especially in examination of patients in "the rheumatic state" It consists of one, two or a shower of circular, elevated, deep red spots, varying in size from that of a pinpoint to 2 mm in diameter, looks like a fresh hemorrhage and fades in 24 hours, perhaps to reappear in different oral situations for as long as two weeks The authors⁸⁴ expressed the belief that it is unrelated to purpura, and that it may be a non-embolic hemorrhagic enanthem It does not exhibit the specific rheumatic lesions

Abdominal symptoms and lesions It is not generally realized that abdominal symptoms are not infrequent in cases of rheumatic fever and that on occasion they are marked, simulating appendicitis, too often leading to negative exploratory operations Guptill⁸⁵ has given these symptoms consideration, describing details of eight cases (from a series of 160 cases of acute rheumatic fever) which simulated cases of acute appendicitis but in which inflammation of the appendix was not proved Four patients were operated on, the appendices were normal In Guptill's cases and in seven similar cases seen by Jones⁸³ the onset of the disease was manifested by fever, pain, nausea, and occasionally by vomiting The pain was in the middle or lower part of the abdomen and was often lancinating It subsided in two or three days in favor of characteristic polyarthritis To distinguish it from appendicitis may be difficult In rheumatic pseudo-appendicitis there is much less vomiting than in appendicitis, abdominal tenderness is present but muscular spasm is absent, and the leukocytes of the blood are increased in number without an increase in juvenile granular cells, the Schilling differential count is normal In appendicitis, vomiting is almost universal among persons less than 20 years of age, and the Schilling differential count is abnormal, for there is an increase in juvenile cells Careful inquiry concerning recent pharyngitis, arthralgia, carditis or previous rheumatism may prevent needless laparotomy When in doubt it is safer to risk negative exploration of a rheumatic patient than to overlook possible appendicitis Some writers believe such pseudo-appendiceal pain is referred from the pleura

In two additional cases of Guptill, true suppurative appendicitis was proved at operation in the course of rheumatic fever A few cases of true peritonitis attributable to this disease have been reported and probably are more common than is supposed In one such case Rhea⁸⁶ noted plaque-like areas on the lateral and posterior peritoneal surfaces, the lesions were similar to Aschoff bodies The intestines and mesentery were congested and edematous

With periarteritis nodosa, abdominal symptoms may be notable Ulceration of the intestine from arterial necrosis and occlusion often has pro-

duced diarrhea simulating that of ulcerative colitis. In two cases of periarteritis nodosa with rheumatic heart disease seen by Friedberg and Gross⁷⁷ abdominal symptoms dominated the clinical picture and led to exploration. These authors expressed the belief that such a complication may be the organic basis for some cases of "abdominal rheumatism."

[The diffuse hemorrhagic changes which, as noted in our last year's review, Collis believed were responsible for acute abdominal symptoms in three cases in which exploration was made are not mentioned in these various reports—Ed.]

Laboratory Data Sedimentation Rates, Blood Counts, Electrocardiograms Blood counts of course should be made in cases of rheumatic fever. Lymphatic leukemia may occasionally simulate rheumatic fever.

[See later, herein, the note of a case described by Sutton and Bosworth, also, see notes on cases of aleukemic leukemia and leukopenic myeloid leukemia simulating rheumatic fever, in last year's review—Ed.]

Previous opinions on the sedimentation rate have been confirmed^{55, 87, 88, 89}

The rate is elevated in rheumatic fever and rheumatic carditis, it varies with the activity of the disease and affords one of the most delicate gauges of activity. It is normal in cases of uncomplicated chorea. However, it is elevated in cases of chorea with carditis, changes occurring even before the carditis is distinguishable. Because uncomplicated chorea is associated with a normal rate, Elghammer⁸⁸ suggested that it may not be a true rheumatic lesion, and Warner suggested that chorea is not an infective process although associated carditis is. According to Struthers and Bacal,⁸⁷ and to Perry,⁸⁹ the rate returns to normal or goes to less than normal with the onset of congestive cardiac failure with edema, a sign of bad import. Elghammer stated that when the rate increases after removal of foci of infection he suspects reactivation of infection.

Alterations in the rate in rheumatism result from a fall in the concentration of albumin in the blood, a rise in globulin, and alterations in the albumin-globulin ratio.⁸⁷

Rheumatic children give no significant statistical variation from normal children, with regard to acidity and total chloride of gastric content, although the former exhibit greater variations on either side of mean values, according to Ogilvie.⁹⁰ The pH of the urine of rheumatic children is similar to that of normal or asthmatic children, even though the former show a higher excretion of various urinary acids.⁹¹

[This work does not seem to us to have been well controlled—Ed.]

Values for blood lipids of children who have acute and chronic rheumatism were found by Kaiser and Gray⁹² to be essentially the same as those of normal persons or of patients convalescing from scarlet fever, but the standard deviations were much greater for those who had the two diseases than for normal persons.

Electrocardiograms Prolongation of the A-V conduction time and

alteration of rhythm are the best known electrocardiographic changes of acute rheumatic fever. Changes in the S-T segment and the T-wave are probably as characteristic and frequent, although they are not pathognomonic. Alterations reported by Easby and Roesler⁹³ and by Kohn⁹⁴ indicate that during the active stage the T-wave may be rounded and small, sometimes iso-electric, diphasic or inverted, and that during recovery it may become upright, tall and sharply peaked before returning to normal. In both reports it is noted that changes similar to those of coronary disease occur and it is suggested that they may result from alterations in coronary circulation, with consequent interference with myocardial blood supply.

Course of the Disease, Evidences of Activity or Reactivity The average duration of the disease, according to Olesen,⁶¹ is 17 years. Kaiser⁶⁵ studied the course of 564 children for three years. Within that time, 49 per cent had recrudescences, particularly those who had chorea. Within the first three years, 5 per cent died. Between the third and fifth years of the disease, 40 per cent had recurrences but only 1 per cent died. Within the first 10 years, 6 per cent died, 25 per cent had recurrences. After the first five years, the prognosis for ultimate recovery and freedom from recurrence is definitely improved. Of Simmons' 206 patients who had carditis, 17 per cent died, their average age was 33 years at death.⁵⁸

Estimation of activity of the disease must always be made in absence of effects derived from salicylates or other antipyretic drugs. Evidences of continued or renewed activity include loss of weight, pallor, fever of low grade, abnormal pulse rate, fleeting muscular and joint pains, tonsillitis, epistaxis, abdominal symptoms, cutaneous lesions, increased cardiac force, transient pericardial friction, electrocardiographic alterations, leukocytosis and increased rates of sedimentation^{66, 95}. Evidences of quiescence include steady gain in weight, slowing of pulse rate to normal, lack of extension of cardiac signs, absence of nodules or of chorea and fall in rate of sedimentation.⁷¹

Comparison of Rheumatic Fever with Tuberculosis and Atrophic Arthritis Cecil again has reminded us of certain relationships between rheumatic fever and atrophic arthritis: both are prevalent in cold, damp climates and rare in the tropics, both progress with exacerbations and remissions, both attack joints and resemble chronic infections, both are associated with foci of infection, iritis, and nodules, both present proliferative and exudative granulomatous lesions—one involving chiefly the vascular system, the other, the joints, and, according to Cecil, both seem related to streptococci.

Similarities between rheumatic fever and tuberculosis have been pointed out for years. Recently (1932) Reitter and Lowenstein reported 70 per cent positive cultures for bacilli of tuberculosis in the blood of patients who had rheumatic fever. If the condition is related to tuberculosis, tuberculin reactions of rheumatic patients should be significant. Pascher⁹⁶ found no differences in the reactions of 245 rheumatic patients and 273 control subjects. Positive reactions were present in about 25 per cent of each group.

Etiology and Pathogenesis Since conceptions of the etiology of rheumatic fever have not changed in any important particular from those outlined in detail in last year's review, we shall note current studies but briefly. The three chief theories continue to be (1) the microbic, (2) the metabolic and (3) the endocrine.

Microbic theory The great majority of writers favor one of the variants of the bacterial theory (1) the theory of bacteremia, (2) the theory of bacterial toxemia, (3) the theory of bacterial allergy. For each group, some hold responsible one bacterium, or its toxin or its antigen, others consider that any one of a number of bacteria, or their toxins or their antigens, may be causal. Highlights in pathogenesis are thought to be preceding tonsillitis or pharyngitis (generally with attendant hemolytic streptococci), a latent period of one to three weeks and then the attacks (fever, polyarthritis, and so forth).⁹⁷ The facts that sore throat so often precedes the initial or recurrent rheumatic attack, and that the disease, always one of low infectivity, occasionally assumes epidemic proportions, strengthen the bacterial theory.

Five varieties of microorganisms have been isolated from the blood of rheumatic patients (1) a "sporulent" bacillus, anaerobic but facultatively aerobic, (2) a diplococcus, aerobic but facultatively anaerobic, (3) a streptococcus, generally hemolytic, (4) diphtheroid organisms (aerobic coccobacilli), (5) enterococci. Such is Bertrand's⁹⁸ grouping. Farah⁹⁹ listed about 25 organisms held responsible at one time or other. Hemolytic streptococci are currently the prevailing culprits, but the majority of writers have hesitated to ascribe more than contributory potentialities thereto, and believe infections therewith precipitate attacks in sensitized persons.^{66, 100}

The bacteremic theory has been supported by Bertrand⁹⁸ who has isolated, from joints and in blood cultures, organisms which, in vitro, change from bacilliform types to diplococci, the cycle—bacillus, diplococcus, coccobacillus, streptococcus—could be developed in either direction. In monkeys inoculated intravenously with these organisms typical acute articular rheumatism developed in 81 per cent of those inoculated with the bacillary form of the organism and in 52 per cent of those inoculated with the diplococcic form. It was concluded that in its virulent state the organism produces acute disease, in its attenuated form, it produces chronic disease. This organism, formerly called "Achalme's bacillus," is now called the "*diplostreptobacillus of rheumatism*." According to Bertrand it is similar to the *Bacillus welchii*.

Howell and Burton¹⁰¹ were unable to "dissociate" streptococci obtained from blood cultures of four patients who had rheumatic fever. The idea of dissociation, or mutation-forms, implies that each bacterium contains a virulent and an avirulent factor. It is believed that the virulent element, or form, of streptococci produces the smooth (S), and the avirulent, the

rough (R) colony. It might be of great clinical value to change the smooth, virulent strain into the rough, avirulent type. Two strains of nonhemolytic streptococci (*Streptococcus salivarius*), one of hemolytic streptococci (*Streptococcus pyogenes*) and one of *Streptococcus viridans* (*Streptococcus mitis*) were recovered in blood cultures. In spite of chemical and physical means, and passage through animals, the strains remained virulent, smooth, and stable for eight months. Howell and Burton concluded that there is little possibility of producing dissociation, a permanent change that occurs in a bacterium and then is transmitted to subsequent generations.

Farah⁹⁹ expressed the belief that the disease is attributable to pneumococci which inhabit the throat and are generally mistaken for streptococci. Intensive studies in a case of pneumococcus arthritis were used in evidence of this idea. We have already mentioned the idea of Reitter and Lowenstein (1932), that the bacillus of tuberculosis is the cause.

[Some of us have been unable to confirm the finding of tubercle bacillema according to their method—Ed.]

The chief proponents of the toxemic theory have been Birkhaug (1927) and Small.¹⁰² Both have lately approved the allergic theory, as have many others^{90, 103}

[*Conclusions on Etiology* It is obvious that the cause of the disease has not been established. The fact that so many different organisms have been isolated and are considered the cause of rheumatic fever suggests that probably no one of those so far isolated is responsible. Rheumatic fever is a fairly distinct disease entity. It would indeed be surprising were it found to be caused by many different organisms—Ed.]

Special laboratory studies. No new studies on blood cultures and agglutination tests are reported. Eighty per cent of a series of 51 rheumatic children were skin-sensitive to hemolytic or nonhemolytic streptococci.⁹⁰ Numerous investigations on throat cultures and on the relationship to rheumatic attacks of infections of the upper part of the respiratory tract have been summarized by Pilot and Davis,¹⁰⁴ by Weinstein and Styron,¹⁰⁵ and by Bradley.⁹⁷ Not all epidemics of sore throat produce initial or subsequent attacks of rheumatic fever. Only a small percentage of patients who have pharyngitis acquire the disease, but those who do acquire it or who already have it seem peculiarly sensitive to nasopharyngeal organisms, chiefly of the hemolytic streptococcal variety. The *Streptococcus epidemicus* (a hemolytic streptococcus) seemed the major invader to Pilot and Davis.¹⁰⁴ Weinstein and Styron¹⁰⁵ made 727 throat cultures of 261 patients (101 patients had rheumatic disease, 160 were controls). Green-producing streptococci were present in all throats, and indifferent streptococci in most. Hemolytic streptococci were found in examination of 43 per cent of the patients who had rheumatic disease and in examination of 31 per cent of the control subjects, and were equally abundant in both. Although the pharyngeal flora of the rheumatic patients was essentially the

same as that of the control subjects, exacerbations of the disease bore a definite relationship to the presence of hemolytic streptococci

Todd (1932) found in blood serum a substance (antistreptolysin, anti-hemolysin) capable of neutralizing the hemolytic substance formed in vitro by hemolytic streptococci. After any infection with hemolytic streptococci, the antihemolysin titer of serum rises materially. Increases were almost always found by him after an attack of acute rheumatic fever, a point in favor of a connection between the disease and hemolytic streptococci. The normal limit was thought to be 50 units. Coburn and Pauli (1932) agreed with these conclusions. Griffiths¹⁰⁶ found high titers (more than 50 units) in work with the serum of the majority of patients, who had subacute rheumatism, infective arthritis, spondylitis, or fibrositis, but generally the titer was normal in cases of spondylitis osteo-arthritis or in cases of osteo-arthritis. This suggests "an association between rheumatic disease and hemolytic streptococci that cannot be ignored." Much higher titers (more than 200 or 300 units) were found in working with the serum of normal persons by Myers and Keefer,¹⁰⁷ and by Wilson, Wheeler and Leask¹⁰⁸. The former agreed that in the majority of cases of rheumatic fever high titers are found, but states that in 21 per cent of them titers were no higher than those seen among normal persons. Furthermore, according to Myers and Keefer,¹⁰⁷ titers of the serum of patients who have atrophic and other forms of arthritis are normal. Wilson, Wheeler and Leask¹⁰⁸ found about the same very wide range of variation in both rheumatic and nonrheumatic patients, and concluded that the results are of no etiologic significance. Titers bore no relationship to the presence of agglutinins and were not related to results of cutaneous sensitization tests.¹⁰⁷

Fibrin of man is normally completely liquefied by filtrates of hemolytic streptococci (Tillett and Garner, 1933). The fibrin of patients recently recovered from hemolytic streptococcal infections is resistant to such lysis. Resistance to fibrinolysis is apparently attributable to production of anti-fibrinolysin and bears a close analogy to the production of antihemolytic antibody. Hadfield, Magee and Perry¹⁰⁹ have noted that patients who have a rheumatic relapse frequently demonstrate total resistance to lysis.

Other theories of etiology. The year's literature affords little support for other than the theory of infection. The metabolic theory was favored by Wainer⁵⁵. At least, Warner expressed the belief that many of the manifestations of the disease (not carditis) are due to causes other than infection, presumably an "altered underlying biochemical state" resulting from dietetic deficiency or imbalance. Rheumatic patients tend to eat too much carbohydrate, too little fat. Dietary correction lowers the tendency to the disease. Llewellyn's⁵⁵ discussion of his ideas along these lines is interesting but highly theoretical.

That rheumatic fever may result from the combined influence of vitamin deficiency plus infection, and from neither factor alone, was the thesis of Rinehart, Connor, and Mettier.¹¹⁰ Guinea pigs subjected to experimental

scurvy (deficiency of vitamin C), and then to superimposed infection, acquired cardiac, articular and other lesions markedly resembling those of rheumatic fever. Minor changes only were induced by either the diet or infection alone. Perhaps latent scurvy of man provides the rheumatic diathesis, conditioning patients to later precipitating infections.

[In a recent discussion on this work it was agreed that changes could be induced but some workers felt that the changes were probably scorbutic, not rheumatic—Ed.]

The combination of experimental deficiency of vitamin A and infection did not produce significant lesions at the hands of Stimson, Hedley and Rose,¹¹¹ but with other dietary deficiencies certain valvular lesions were produced in a few animals. Lesions similar to Rinehart's experimental myocardial lesions in scorbutic guinea pigs were produced by injections of streptococcal exotoxin, without introducing live microorganisms.

Treatment The value of established methods has been reaffirmed, no new treatments were proposed.

Drugs We are again reminded that salicylates are helpful in reducing fever and pain but that they do not prevent or alter cardiac complications.^{95, 112} Fantus¹¹³ advocated amidopyrine when salicylates fail or are not tolerated. Jenkins¹⁰³ expressed the belief that the use of atropine hypodermically is more efficient than salicylates in reducing fever and joint-distress but that it is equally as useless as salicylates for a real cure. The dangers of cinchophen have been overstressed, according to Lawler¹¹⁴ who expressed himself as in favor of the use of mono-iodocinchophen. No relief was received by six patients whom Slot and Deville¹¹⁵ treated with gold (solganol). Untoward reactions may occur therefrom: nephritis and jaundice. Injections of histamine were given by Shanson and Eastwood¹¹⁶ to patients who had subacute rheumatism, moderate relief was noted.

Tonsillectomy The controversy regarding the value of tonsillectomy has continued. The majority of observers favored it. Thus Miller¹¹⁷ expressed the belief that it gives the best chance of safeguarding rheumatic children from the more serious forms of the disease. According to Swift, among nonrheumatic persons, five to 30 years old, who have tonsillitis or pharyngitis, only about 10 per cent may be expected to suffer from definite rheumatic fever, but among those of that age who have previously had rheumatic fever, at least 50 to 60 per cent who acquire infections of the throat will have a new attack of rheumatic fever. Thus the importance of tonsillectomy in safeguarding such patients is obvious. The opinions of Kaiser⁶⁵ are well known: subsequent attacks of rheumatic fever occur slightly more often among children whose tonsils have not been removed at the initial attack. The mortality rate is nearly 50 per cent less among those whose tonsils have been removed before the initial attack. Tonsillitis or sore throat preceded rheumatic fever in 59 per cent of children studied. Although tonsillectomy lessens the mortality and the incidence of the more serious rheumatic manifestations, it does not prevent recurrences. The

views expressed by Coates and Gordon¹¹⁸ were similar. Stahl¹¹⁹ noted no ill effects, but often much benefit, from early tonsillectomy.

Wholesale tonsillectomy is useless, according to Schlesinger⁷¹ and to Poynton,¹²⁰ for pharyngitis affecting a tonsillectomized child can cause rheumatic fever. The tonsils should be removed, however, if they are septic or markedly enlarged, or if the child has repeated attacks of sore throat.

Diet. Poynton¹²⁰ has not noted the reputed dislike of rheumatic children for fat. A diet such as is given in the presence of any febrile disease seemed indicated to Douthwaite¹²¹ but in spite of cellular destruction and loss of nitrogen from fever, he advised not to increase the intake of proteins lest indigestion ensue. For the sickly child an increase in calories may be most helpful.⁷⁰

Rest. The value of prolonged rest was stressed by all writers.

Vaccines, antigens, serums. Contrary to the opinion of many, Wolffe⁹⁵ and Cecil⁵⁶ expressed the belief that streptococcal vaccines are of value in treatment and prophylaxis. Injections of bacterial antigen of *Streptococcus cardio-arthritidis*, in smaller doses than any yet used in biologic therapy, are definitely helpful, according to Small¹⁰². The antigen is diluted to an extent which at first appears to be an absurdity, but control studies convinced Small of their potency and usefulness. Overdosage is followed by prompt exacerbations of rheumatic fever. A discussion of the various reactions to treatment and a detailed plan of dosage are given in the article. In general, the use of foreign proteins is unsatisfactory but occasionally, in obstinate cases, it gives startling results, and stops the acute attack speedily.^{70, 113}

[Some may have a remission shortly thereafter, however—Ed.]

In 12 cases results with streptococcus (scarlatina) antitoxin were encouraging.¹¹²

Climate and institutional care. Convalescent homes constitute one of the greatest advances in the therapy of this disease.^{61, 71} A prolonged sojourn in a subtropical climate may be a "specific." Eleven of 14 patients who had active carditis and who were sent by Nichol⁵⁷ to Miami improved markedly or went into a remission. Roche and Jones¹²² sent to Florida 14 children who had been affected with severe carditis for an average of four years, 12 of them were conspicuously improved. Even after they had returned to New England improvement continued.

Effect of pregnancy. From a study of 40 males (as controls), 28 nulliparous women and 41 parous women who had carditis, Gilchrist and Murray-Lyon¹²³ were unable to show that two pregnancies shortened the life of the rheumatic patient. One or two children may generally be borne without detriment. Similar conclusions were reached by Scott and Henderson¹²⁴, the physical strain of pregnancy can be minimized or counteracted by sufficient rest. If the patient has the means to obtain rest, one or two pregnancies may be permitted. However, repeated pregnancies are not well borne and may provoke fatal cardiac decompensation.

Prophylaxis Prevention of relapses is more likely under the following regimen^{71, 113} a nutritious diet high in vitamins, cod liver oil, tonsillectomy, outdoor life with graded exercises, avoidance of chilling and, above all, of respiratory infections. If the latter are epidemic, avoidance of chilling and of crowds, spacing of beds, isolation from patients who have colds, sterilization of the patient's plates, cutlery, and pencils, concentrated treatment with acetylsalicylic acid for three weeks after an infection of the throat, and a stay in a warm room during such an infection, are indicated. Institutional care or life in a subtropical climate is most helpful in certain cases.

SYDENHAM'S CHOREA

It was accepted by Mutch¹²⁵ and by Copeman¹²⁶ that Sydenham's chorea is related to rheumatic infection, as is indicated by the occurrence of cardiac sequelae in 30 to 40 per cent of cases of chorea. Nervous strain and deficiency of calcium may also be factors¹²⁵. However, since the sedimentation rates are generally normal in cases of chorea not accompanied by carditis, some investigators⁵⁵ have expressed the belief that the condition may not be infective, although complicating carditis probably is. The average duration of the disease is about 27 days in mild cases, 44 days in moderately severe cases and 62 days in severe cases^{125, 127}. Copeman expressed the belief that it lasts more nearly three months than six to ten weeks as generally is stated.

Treatment The therapy of the past was outlined by Mutch¹²⁵. Three newer contributions to the therapy of chorea are the use of the sodium salt of phenyl-ethyl-hydantoin (nirvanol), of ketogenic diets, and of typhoid-paratyphoid vaccine. Mutch and others got little result with diet. It has been noted repeatedly that patients who have chorea have been benefited by intercurrent fever (Turnovszky, 1930) and that measures which help most in chorea are accompanied by fever. Various methods of fever therapy have accordingly been advocated: the use of nirvanol (Roeder, 1919), auto-serum (Brown, Smith, Phillips, 1919), chemical protein (Horton, 1922), fever reactions with milk (von Kern, 1923, Hymanson, 1926), *Typhoid-paratyphoid vaccine* (Mas de Ayala, 1930), typhoid-paratyphoid vaccine (Sutton, 1931, Trawley, Pepper and Wathe, 1932, Bateman, 1933).

[More recently, fever machines and colloidal sulphur have been employed. Reports on these belong in our next review.—Ed.]

Nirvanol The usual nirvanol reaction includes drowsiness, headache, fever, rash, eosinophilia and leukopenia, the fever presumably is the useful component. Untoward reactions may occur: purpura, jaundice, diarrhea, nephritis, incontinence of urine, enlargement of the spleen and liver, prolonged high fever, coma and occasionally death^{125, 128}. Of 28 cases in which Silber and Epstein¹²⁹ administered treatment, in 10 improvement was prompt, choreiform movements stopping completely. In 18 there was no improvement, in nine of these cases the reaction failed to develop. Asso-

ciated carditis is not affected by the treatment Marick¹³⁰ noted improvement in the majority of 55 cases in which treatment was given. However, two to three years later some of the patients had recurrences, others, dyspnea, many were still nervous. Recurrences therefore apparently are not prevented by nirvanol. Its value was accepted by Call¹³¹ with reservations. Of 26 patients, 18 were markedly improved in 10 days, five became free of symptoms in 20 days. In one case, adenitis, ulcerative stomatitis and gingivitis, and ulcerative conjunctivitis developed but the patient recovered. In spite of these and other favorable reports (Pilcher and Gerstenberger, 1930), the Council on Pharmacy and Chemistry of the American Medical Association has not seen fit to accept the drug (1932). Mutch¹²⁵ expressed the belief that the use of nirvanol is dangerous, Copeman¹²⁶ found it of little value. Don¹²⁸ stated his belief that generally it can be given with confidence, however, he noted prolonged, persistent fever in one case.

Typhoid-paratyphoid vaccine. The advantages of febrile reactions produced by vaccine were first reported by Sutton (1931). A second report¹²⁷ concerned 150 patients so treated and 150 patients treated otherwise. By inducing fever with the vaccine, the duration of mild cases was shortened (as compared with those treated otherwise) from 27 to six days, moderate cases, from 44 to nine days, severe cases, from 62 to 16 days. The average number of treatments required was six (from three to 18), they were usually given daily. In only 10 per cent of cases was the result disappointing. No untoward reactions were encountered. Active carditis was not a contraindication, indeed, it seemed to be benefited. Capper and Bauer¹³² induced 297 reactions in 23 cases (generally in series of one each day for one week). The disease in these cases had lasted from four months to four and a half years. Marked improvement in some, and in several prompt cures were obtained and were maintained many months. Equally impressive results were obtained by Fish¹³³ and by Redfearn¹³⁴ in one case each, and by Hoverson¹³⁵ in two cases. Hoverson also treated four patients who had Huntington's chorea, two completely recovered, two were unrelieved.

Comparing the results from the use of typhoid vaccine (23 cases) with those obtained with nirvanol (24 cases) Montfort¹³⁶ strongly favored the former on the grounds that it shortens the course of the disease, is harmless, is followed by a significant lack of recurrences and sequelae, and is easy to administer. With nirvanol, which was definitely helpful, the disease lasted an average of 24 days, with vaccine, 16 days. Marick on the other hand felt that each was helpful but that nirvanol was safer.

Other medicines. Believing that a disturbance of calcium metabolism occurs with chorea, Mutch¹²⁵ prescribed calcium-acetylsalicylic acid, 60 grains (4 gm.) daily. The nervous manifestations were controlled after an average of 17 days (7 to 46 days).

CHRONIC ARTHRITIS

Introduction and Terminology Because of its frequency and the chronic disability which it produces, chronic arthritis in conjunction with fibrositis has an enormous morbidity rate. The economic importance of this disease is greater than that of tuberculosis, heart disease and cancer combined.^{2,4} When the term "chronic arthritis" is used, it generally refers to "atrophic arthritis" or "hypertrophic arthritis" or to both forms undifferentiated, all other forms of chronic arthritis such as tuberculous, gonorrheal, traumatic, or gouty arthritis are, or should be, tacitly excluded. In this review, regardless of the terms used by authors quoted, we shall use the nomenclature adopted by the American Committee,¹³⁷ according to which "atrophic arthritis" is employed as synonymous with "chronic infectious," "proliferative," "type one," "synovial" and "rheumatoid arthritis", and "hypertrophic arthritis" as synonymous with "chronic senescent," "degenerative," "type two," "chondro-osseous arthritis" or "osteo-arthritis". Terms approved by the committee as a group are not necessarily those individually preferred by members of the committee or by the editors of this review. It is assumed that the reader is familiar with the basis of these terms and with the various criticisms thereof.^{4, 137, 138, 159} Each term has its merits and its demerits. Under certain circumstances a pathologic term may be preferable, under other conditions a clinical term seems best, it is important for the reader to recognize their synonymy.

Etiology, General Remarks Current reports continue the arguments as to the relationship between the two great types. The majority of authors feel that the two are so different in clinical, chemical, roentgenologic, and pathologic manifestations, as well as in prognosis, that they must be considered separately and must represent two distinct diseases. Others believe that the two are merely different manifestations of the same fundamental disturbance and that their obvious differences arise merely from the factors of the patient's age at the time of onset of the disease, of his physique (asthenic or hypersthenic constitution) or because of differences in the reactions of various individuals to the same insult. Still others believe that the so-called differences are more imaginary than real, and that there is but one type which may, however, arise from one or several causes. Regardless of whether the two types have a common etiology, the great majority of writers insist that clinically they are sharply distinct.

Strictly speaking nobody, of course, confines himself to a belief in one solitary cause. All recognize the interdependence of seed and soil, but opinions differ as to whether abnormality of the seed or of the soil is the more important, and as to what is the essential cause without which, regardless of the presence or absence of contributory or precipitating factors, the disease could not eventuate. At times the contention simulates the one on the priority of the hen or the egg. Those who favor the theory of infection ascribe primacy to the seed and believe that a microorganism is the essential cause,

although admitting the need for a proper soil. Those who favor the "metabolic theory" generally admit the secondary importance of focal or other infection but lay stress on physiologic alterations which prepare the soil for various bacteria to produce arthritis. The two viewpoints are by no means as antagonistic as some would believe. The adherents of each are probably but facing each other, perhaps at times a bit angrily through the same window.

Those who favor the idea of separate types and of the probability of a separate cause for each type are too numerous to mention but include, in this country, Bauer, Boots, Dawson, Cecil, Ghrist, Hall, Hench, Holbrook, Key, Miller and many others.

Those who favor the clinical separation of the two types but believe that both may have the same cause, or very closely allied causes include, in this country, Fletcher, Osgood, Pemberton, White and many others. Adamson⁶ expressed his viewpoint thus: "As champagne or port wine will do nothing to one person, give another gout and give a third a headache so streptococci on a soil previously prepared by intestinal toxemia may produce rheumatoid (atrophic) arthritis in one, (hypertrophic) osteo-arthritis in another, fibrositis in a third, one of the differences being not in the bacterial invasion but in the physico-chemical or 'electro-chemical' state of the tissues."

[The analogy is interesting but is worthy of criticism. Nobody believes that champagne and wine are causes of gout. They merely act as one of many widely different predisposing or precipitating factors. Much confusion is fostered by such statements in which writers do not assiduously differentiate in their papers, or even in their own minds, between what are merely inciting or predisposing factors and what should be considered the actual etiologic factor, the *sine qua non*. Were the numerous secondary factors in the production of the chronic arthritides not so often thoughtlessly or carelessly raised to the status of prime cause, there would not be so many theories and variants thereof to pester us—Ed.]

R and J Kovacs¹⁴⁰ argued that a streptococcal infection of low grade is present in both types of arthritis, the type resulting depends on the patient's constitutional configuration—atrophic arthritis in the asthenic, hypertrophic in the sthenic type. Sherwood's¹⁴¹ therapy is based on the idea that both, and also the menopausal type, are of infectious origin.

[No proof is offered regarding etiology. "Menopausal arthritis" is not a clearly defined entity—Ed.]

Brooks¹⁴² expressed the belief that both are infectious but that atrophic arthritis is probably streptococcal, hypertrophic arthritis staphylococcal, in origin.

[This is the exact opposite of Crowe's ideas, 1930—Ed.]

According to Haden¹⁴³ the fundamental factor in both types is probably a disturbance in capillary circulation. Elsewhere, however, Haden^{144, 145}

has seemed to favor the theory that any one of a number of different causes may produce either type of arthritis

Those who would reunite the two types under one heading, and who favor a unity of causation, include Archer, Burbank, Clawson and Wetherby, Knaggs, Willcox, and Wright. According to Archer¹⁴⁶ the (unstated) cause of both may be the same, since, in a somewhat analogous manner, syphilis can cause either a proliferative (syphilitic) arthritis or a degenerative arthritis of the Charcot type. Wetherby¹⁴⁷ was unable definitely to segregate atrophic or hypertrophic arthritis or even rheumatic fever one from another because of the clinical, humoral, radiologic, and pathologic similarities which he found they exhibited. He expressed the belief that all are probably streptococcal. In his opinion chronic arthritis may often result from an acute attack indistinguishable from rheumatic fever.

[Shapiro,¹⁴⁸ in the same city, studying "several hundred cases" of rheumatic fever from childhood to adulthood, found no instance wherein chronic arthritis directly followed rheumatic fever—Ed.]

Burbank¹⁴⁹ expressed the view that chronic arthritis is caused by an infection, the chief offenders are streptococci, not of a specific strain, together with a variable, "X." The latter factor may be dietary defect, endocrine abnormality, sensitization, depletion from some intercurrent cause, mental and physical trauma, faulty posture, or some other abnormality. While infection may play a rôle in each type of chronic arthritis, a nutritional change, probably a vitamin deficiency, is the fundamental cause of both, according to Wright¹⁵⁰, the difference mainly arises from the variable reactions of different people.

[Again no proof whatever is offered—Ed.]

The idea of one clinical type produced by various causes is again advocated by Nissen,¹⁵¹ Nissen and Spencer,¹⁵² and Ober.¹⁵³ Accepting the concept that chronic arthritis is one disease, Nissen expresses the belief that variations are a matter of individual reaction and that the very multiplicity of functional disturbances points definitely to the conclusion that there may be no one etiologic agent. With this Ober agrees, although elsewhere he and Burnett¹⁵⁴ have suggested that "non-specific arthritis" is a deficiency disease.

[Data given do not permit this conclusion. True arthritic changes, as contrasted to scorbutic changes, have never been clearly demonstrated in animals on diets variously deficient—Ed.]

Arthritis is not a disease, per se, according to Wolf,¹⁵⁵ but a symptom—an expression of an inflammatory reaction to an infinite number of factors.

[The editors cannot but feel that, regardless of etiology, the two diseases are separate and not merely different manifestations of the same process among persons of different age groups. Classical atrophic arthritis frequently is seen just appearing when patients have passed the age of 50, 60 or 70 years. Atrophic arthritis at this

stage is essentially the same as it is at the age of 20 years. Conversely, not infrequently one sees cases of premature senescent arthritis—typical hypertrophic arthritis with Heberden's nodes—affecting a woman 30 to 35 years of age. Thus, too, rheumatic fever occasionally may first appear in a person past 50 years of age. Although minor variations appear in adult rheumatism as compared to juvenile rheumatism, the two chief characteristics of the disease, carditis (not endocarditis) and articular resolution without chronic arthritis, are manifest in both groups, regardless of age. It is admitted that the patient's tissue-age and chronologic age are not necessarily identical but it seems apparent that, regardless of age at onset, the two diseases tenaciously retain their distinct identity too often for us to accept the idea that the varying clinical expression of arthritis is conditioned by age only, either tissue-age or chronologic age. It is understood, of course, that the editors recognize the differences between clinical hypertrophic arthritis, one disease, and radiologic hypertrophic arthritis, several diseases—Ed.]

The terminology favored by individual writers depends of course on their ideas on etiology. If they are sufficiently convinced of the bacterial causation, they call the condition "infectious arthritis", otherwise they rely on less committal terms based on pathologic, radiologic or clinical differences. Brooks¹⁴² subdivided streptococcal rheumatic disease on anatomic grounds into types affecting various tissues such as mucous, dermal, connective, fatty, muscular, cardiac, nervous, glandular, ocular, otic, and articular tissues. Others also (Fisher, 1929) have subdivided "chronic arthritis" into synovial (atrophic) arthritis, or chondro-osseous (hypertrophic) arthritis. Another writer¹⁵⁶ has proposed a numerical and alphabetical system as a simplified means of recording the various etiologic factors: allergy, bacteria, climate, diet, endocrine abnormalities, fatigue, gastrointestinal disturbances, trauma, nervousness. The unknown factor, "X," is the soil. If "B" signifies bacteria, "E" endocrinopathy, "N" nervous disturbance, and "T" trauma, and the patient has such abnormalities, his formula reads Patient = X (B + E + N + T).

[Such a "simplified" concept seems more ingenious than practical—Ed.]

DISTINCTIONS BETWEEN THE TWO TYPES CLINICAL, PATHOLOGIC, AND RADIOLOGIC

The accepted distinctions between the two types were outlined fully in the first review⁴ and in the Primer¹³⁷ and will not be repeated here. Gelber and Goldberg¹⁰ reviewed the usual roentgenologic differences, using Goldthwait's¹⁵⁷ classification, in which rheumatoid arthritis is subdivided into "infectious arthritis" and "atrophic arthritis."

[Here as elsewhere the roentgenologic subdivision seems not clear, and unnecessary—Ed.]

Various roentgenographic alterations are common to all types of arthritis, according to Taylor, Ferguson and Kasabach,¹⁵⁸ and there is no one diagnostic feature in any. However, each type has a characteristic combination of alterations that makes a roentgenogram valuable in diagnosis.

To venture a clinical or etiologic diagnosis, the roentgenologist should at least be told the duration of the disease. The roentgenogram in a case of fairly early gonorrheal destructive arthritis may simulate that of late tuberculous destructive arthritis. In roentgenograms, atrophic and hypertrophic arthritis appear to be distinct entities. Both may affect the same joint, even so, the characteristics of each type are generally demonstrable. The constancy of the findings in cases of atrophic arthritis does not favor further subdivision of this group.

ATROPHIC (INFECTIOUS, PROLIFERATIVE, RHEUMATOID) ARTHRITIS

Symptoms and Course In some cases the onset is abrupt, with an acute, febrile reaction, considerable articular heat, redness, swelling and other constitutional signs of infection, this subtype is often distinguished from the more chronic variety and has been called "subtype a" by Holbrook,¹⁵⁹ "group one" by Cox and Hill,¹⁶⁰ "secondary rheumatoid arthritis" by Buckley¹⁶¹ and "infectious arthritis" by Senturia.¹⁶² This variety of the disease is generally attributed to infection. Foci of infection are usually to be found and their removal may cause prompt and notable improvement, with early cessation, instead of an indefinite, smouldering progression of the disease.

In the majority of cases, however, the onset is insidious and relatively afebrile, joints are affected somewhat symmetrically, foci of infection either are not found or their removal gives little relief. This major variety has been called by various authors "subtype b,"¹⁵⁹ "group two,"¹⁶⁰ "primary rheumatoid arthritis,"¹⁶¹ and "atrophic arthritis."¹⁶²

Usual symptoms of the disease need not be listed again here.⁴ Wetherby again has reported his analysis of 350 cases (1932 and 1934¹⁴⁷) of chronic arthritis but since cases of both types were indiscriminately included, the analysis does not lend itself to comparison with others.

[Even though an author believes in unity of cause, for the sake of comparative statistics he should include a clinical differentiation, otherwise his data are practically useless—Ed.]

Acute rheumatoid (atrophic) arthritis and Still's disease are one and the same, according to Moltke¹⁶³ who reported four cases of the former (adult Still's disease) in males, aged 15 to 28 years. Common characteristics were subacute, sometimes remitting, fever, peri-arthritis with fusiform swelling, poly-adenitis (in 37 per cent of a larger group of cases of atrophic arthritis), anemia, muscular atrophy, sweats, increased rate of sedimentation, and chronicity. Splenomegaly is not a requisite for Still's disease, it was absent in three of Still's 10 cases. Serositis of the pericardium, pleura, and peritoneum are variably present in Still's disease, they are rarely found in atrophic arthritis. Splenomegaly in cases of juvenile Still's disease represents a physiologic response more common in children than in adults.

Of four cases of *scleromalacia perforans* (various-sized holes in sclera without dominant signs of inflammation) reported by van der Hoeve,¹⁶⁴ in three the patients were women who had advanced atrophic arthritis. Perhaps both affections have a common cause.

Nissen¹⁵¹ and Nissen and Spencer¹⁵² expressed the belief that "individual reactions" rather than factors of heredity, environment, focal infection, worry, age of onset, severity or duration of arthritis, or treatment determine the prognosis. Following the course of 95 patients with different types of arthritis to their deaths, these authors found that four life courses were graphed regardless of the type of arthritis present. Course A is that of the patient who, with the onset of arthritis, drops to some lower level of activity. He remains there for a time, and then, because of better tissue inheritance, determination, successful therapy, or natural individualistic reaction, he climbs back to the former level of activity and remains there for the rest of his life. The average duration of life after the onset of the disease was 27 years. In course B the patient, after his initial attack, experiences remissions and relapses, the latter increasing in duration and frequency, the mean course is a slow, steady decline. The average duration of life after the onset was 17.3 years. In course C the patient progresses until he receives a severe systemic upset, perhaps an infection, then rapidly polyarticular destruction develops, at which level of crippledness he may remain, with little variation in his arthritis, he may survive long at a minimal level of function. The average duration of life after onset was 19 years. In course D the disease develops acutely or insidiously, it progresses with variable rapidity, the life course dropping steadily to death, in such cases surgical measures may be dangerous. The average duration of life after onset was seven years.

[Such figures as the authors gave, mixing various types of arthritis—atrophic, hypertrophic, mixed types, gonorrheal, tuberculous and rheumatic fever—all together are unfortunately of little value. It might be said that a patient who has almost any chronic disease, regardless of all other factors, will (a) soon get well, (b) slowly get worse but not die, (c) rapidly get worse but not die, or (d) die fairly soon. After all, there are no other possibilities. However, such few statistics as the authors gave on the course of the separate types represent valuable information. The authors must have some very useful information were it restated—Ed.]

Of 27 patients who had atrophic arthritis (type I) 4 per cent (one case) followed life-course A, 36 per cent (10 cases) course B, 30 per cent (eight cases) course C and 30 per cent (eight cases) course D. In comparison, 3 per cent (one case) of 30 patients who had hypertrophic arthritis (type II) followed course A, 70 per cent (23 cases) course B, none course C, and 20 per cent (six cases) course D.

[This statement is not clear. It implies that in certain cases hypertrophic arthritis leads to fairly rapid death, an untenable idea—Ed.]

Of 26 cases of mixed (atrophic and hypertrophic) arthritis, 12 per cent (three cases) followed course A, 46 per cent (12 cases) course B, 15 per cent (four cases) course C, and 27 per cent (seven cases) course D. Of eight cases of Strumpell-Marie's disease (atrophic spondylitis) 80 per cent (five cases) followed course B and 20 per cent (three cases) course D.

The effect of intercurrent disease (tuberculosis, syphilis, pernicious anemia, gout, psoriasis, diabetes, and hyperthyroidism) on the course of atrophic arthritis was discussed by Cecil¹⁶⁵ who expressed the belief that atrophic arthritis rarely but occasionally occurs in association with tuberculosis, he gave examples of the coincidence of arthritis with the diseases mentioned.

Pathology The pathologic distinction between atrophic and hypertrophic arthritis has been fully given^{4, 137, 138, 139} and has been reviewed by Pemberton and Bach¹⁶⁶. No new work was presented.

Routine Laboratory Data In atrophic arthritis (18 cases) according to Steinberg¹⁶⁷ the average leukocyte count is higher than it is in hypertrophic arthritis (26 cases), in the former there is a definite tendency for the Schilling differential count to shift to the left. This fact may be helpful in differentiation. Persistent eosinophilia of 5 to 8 per cent may occur in severe cases. As does the sedimentation rate, so does the nuclear count in atrophic arthritis reflect the severity of the disease to a great extent and together with the rate of sedimentation, the nuclear count can be used as an index of activity, according to Rawls, Gruskin, Ressa and Jordon¹⁶⁸ who studied 263 determinations of the rate of sedimentation and 258 nuclear counts in 50 cases. The value of the rate of sedimentation has been similarly confirmed by Stainsby and Nicholls¹⁶⁹ who, using the corrected sedimentation index of Rourke and Ernstene, noted that the average rate increases with the patient's age and tends to be lower in summer than in winter. Changes in the agglutinin titer for hemolytic streptococci appear and develop slowly, they are not related to the activity of the disease and no correlation between them and the sedimentation rate exists. A method of determining the sedimentation rate with blood obtained from a pricked finger, without venipuncture, was described by McSweeney¹⁷⁰.

Degenerative diseases are more likely to be associated with hypercholesteremia than are inflammatory diseases, which are often associated with hypocholesteremia. Some significance may be attached, therefore, to the finding by Bruger and Poindexter¹⁷¹ that in seven cases of hypertrophic arthritis the concentration of plasma cholesterol was higher (178 to 441 mg per 100 c.c.) than it was in three cases of atrophic arthritis (168 to 229 mg per 100 c.c.). These findings were confirmed in the larger series of Hartung, Greene and Bruger¹⁷² (33 cases of atrophic, 59, of hypertrophic arthritis). The concentration of serum calcium in atrophic arthritis is essentially normal, in hypertrophic arthritis it is slightly but significantly increased, an increase not attributable to age¹⁷².

Etiology and Pathogenesis In general the year's literature presents no

significant modifications of the outline and schemes given in last year's review. Current theories remain (1) that of infection with the three variants, (a) bacteremia, (b) bacterial toxemia, and (c) bacterial allergy, (2) that of metabolic abnormality with its numerous variants such as the ideas of (a) deranged metabolism of carbohydrates, (b) deranged metabolism of protein, (c) deranged metabolism of sulphur, (d) food allergy, and (e) vitamin deficiency, (3) the theory that circulatory imbalance or deficiency leads to articular "blood hunger" and consequent arthritis, and (4) the theory of endocrine abnormality. Writing on the etiology and pathogenesis of arthritis, investigators in the past have, of course, recognized the interrelationship of three factors (1) the predisposing factor, soil, (2) the true or fundamental etiologic factor, generally thought to be a micro-organism, and (3) the precipitating factor, such as shock, grief, nervous fatigue, endocrine crisis and so forth. Thus, there has been formed the useful equation of the causal factor as the numerator, and the person's resistance (soil) as the denominator. When the value of the denominator is equal to, or greater than, that of the numerator, arthritis does not occur, regardless of foci of infection and so forth. When the balance is upset by an increase in the numerator (added infection) or by a decrease in the denominator (a change in the patient's resistance making the soil proper for the development of the disease, the soil perhaps altered as a result of some precipitating factor) then arthritis may occur. Tacitly admitting the importance of all these factors of the equation, writers, nevertheless, have been inclined to stress sharply the overwhelming importance of the seed—the fundamental factor without which arthritis cannot develop regardless of soil, precipitating factors or other factors. In articles of the past, the tendency was for the author to state rather boldly what he believed the main cause of the disease to be, whether infection, metabolic abnormality, endocrine disturbance, or neurogenic disorders, and for the author to give but little recognition to the arguments of others.

In current literature a subtle change is evident. It is rare now to read the blunt statement "a germ is responsible" or "circulatory derangements are the cause." Now, while still defending the claims of their favorite causal factor, writers are admitting the significance of other factors. Speaking with less assurance on their favorite theme, they are careful to erect a small monument to the unknown god of others. They resemble the roulette player, who, after carefully placing his chips, tosses a precautionary one on the 0 or double 0 just before the "rien ne va plus." Thus splitting their ticket, they are taking the best from each theory to support the eclectic theory that there is probably no one cause for the disease and that any one of a number of causes may be responsible.^{143, 173}

This indicates a growing tolerance, perhaps a broadening of vision, but it has not yet led to increased clarity of ideas, rather the opposite. For during this stage of transition the literature has become less clear, ideas are less concise and it becomes increasingly difficult to catalogue a writer. One phy-

sician wrote "There is no one cause for chronic non-specific arthritis of either type. Perhaps most cases result from the interaction of several factors. It is quite probable that a disturbed circulation is often the primary disturbance."¹⁴⁴ But elsewhere¹⁴³ he wrote, "There is not one cause for chronic rheumatism. Perhaps most cases result from the interplay of several factors. Infection is the most important factor in the atrophic type." And again,¹⁴⁵ "Possibly the disease (atrophic arthritis) cannot develop in the absence of bacteria but the presence of bacteria alone is insufficient in most cases to produce the disease, so other factors are of equal or greater importance." Thus it is difficult to know just what the writer believes on causation, but it is evident that he, long a thoughtful student of the subject and once a firm believer in the theory of infection, is becoming less certain of the rôle of bacteria in arthritis. This state of affairs, confusing and fruitless at the moment, presages advance, because it indicates dissatisfaction with current ideas.

[The eclectic theory does not satisfy the editors of this review. A disease as consistent in its manifestations and course as is atrophic arthritis is assuredly not caused one day by this, the next day by that, factor. Granting the soil and other predisposing, precipitating and aggravating factors all the importance they deserve, there surely must be one prime cause, "X," without which the disease cannot begin or continue. Current confusions, including ideas on polymicrobial origin, are entirely analogous to those held in regard to tuberculosis before the "X" of that disease, the bacillus of tuberculosis, was finally isolated.—Ed.]

Factor of heredity Buckley¹⁶¹ stated that heredity is a factor in about 50 per cent of cases and that, probably because of endocrine influences, sympathetic instability, and defective assimilation of calcium, the bodily characteristics of the candidate for arthritis are a slight, spare physique resembling that of persons who are prone to acquire tuberculosis. Walker¹⁷⁴ also stressed the congenital nature of the disease and gave family charts of 13 patients, five of whom had arthritis. He suggested that arthritis is a congenital abiotrophy, resulting from the union of unsuitable types—the union of short and tall persons, of persons with different blood groups, and of persons with straight and with wavy hair.

[Blood groups in 1000 cases studied by Race¹³⁹ were what might be expected from a sampling of the general population.—Ed.]

Walker wrote "These people inherit the diaphyses of all or part of their bones from one racial element and the epiphyses from another. Sometimes this inheritance is one-sided. The receptivity of these tissue-masses cannot be expected to be the same to a given hormone." By some process of reasoning Walker deduced that therefore the pancreas has to work overtime and becomes exhausted. Hence improvement may follow the use of pancreatin and a starch-free diet. In one of Cecil's families the disease was traced through four generations.¹⁶⁵

[We believe that statements like the above will lead the reader to agree with Cecil that remarks on the hereditary nature of arthritis are usually very loosely presented and unsupported by accurate data. Of course almost every family presents arthritis and many are riddled with senescent arthritis if with no other form. Statistics on heredity and arthritis are erroneous because generally data on the type of arthritis present are not given.—Ed.]

Factor of infection That some infection, probably streptococcal, is the major factor is still the belief of the majority, and the familiar arguments are presented by many. Buckley,^{39 161} Cecil,¹⁷⁵ Sprunt¹⁷⁶ and Burbank¹⁴⁹ Cecil, Griffiths,¹⁹⁰ and Dawson, Olmstead and Jost¹⁷⁷ are among those who incriminate hemolytic streptococci. The bacteremic variant of the infectious theory is held by Cecil and by Burbank. The latter has expressed the belief that although the streptococcus is the chief offender, it is not a specific strain but one which has developed the power to ferment mannite and to live in the presence of a comparative deficiency of oxygen. Such organisms possess definite powers of adaptation and mutation, and may reduce their chains to appear as diplococci, or may dissociate into diphtheroid forms, or even may appear as staphylococci similar to Crowe's *Micrococcus deformans*. According to Burbank, the power of adaptation is shown by the fact that the apparent focus of infection rarely contains a streptococcus similar in type or in power to ferment sugar to that isolated from the joints at biopsy. The organism changes its nature from one with invasive properties to one more parasitic in nature, thus avoiding the strong immunologic reactions of the host, which would kill it.

The idea of specific bacterial toxemia apparently has been abandoned in favor of that of bacterial allergy from one or from multiple strains of streptococci or other bacteria. The basis for this idea has been reviewed by Hitchcock¹⁷⁸ indirect evidence based on cutaneous reactions, variability in cultural results, supposed desensitization by the use of bacterial antigens, and so forth. On the basis of skin tests, Wainwright¹⁷⁹ has tentatively accepted the idea of bacterial allergy. From 94 blood cultures made in 91 cases of atrophic arthritis he recovered streptococci (viridans) in only one case, diphtheroid organisms in four cases and contaminants in seven cases (staphylococci four times, gram-positive bacilli three times). In 14 cases cultures of joint tissues were made in 12, these cultures were negative, in two, molds were found. The serums in 46 (90 per cent) of 51 cases were found to possess agglutinins for hemolytic streptococci in dilutions varying between 1 to 20 and 1 to 1280. Thus the extent of the dilution was somewhat lower than that reported by others. The presence of such agglutinins in serum of patients who have this disease seems well established, but this does not of necessity indicate a causal relationship. As has been suggested by others, agglutination may be attributable to the presence of natural, not acquired, or specific agglutinins, but the frequency with which it occurs is to Wainwright the best evidence thus far produced that the streptococcus is the cause of the disease.

All of Wainwright's 55 patients who were tested gave positive cutaneous reactions to one or more strains of hemolytic or green-producing streptococci. Whole organisms were used. In 24 cases the reactions were positive to hemolytic streptococci only, in three, to *Streptococcus viridans* only, and in 28 to both types. In 90 per cent maximal reactions were to the hemolytic type, in 10 per cent to viridans, but no single strain predominated in causing maximal reactions. When cutaneous sensitivity exists it does not necessarily also indicate articular or general sensitivity. Objections raised to the interpretation of cutaneous reactions to autogenous vaccines, that they may indicate varying irritability of the patients' skins, natural toxicity of the bacterial species, or perhaps sensitization to certain bacterial groups, must be considered.

Further indirect evidence of a relationship between hemolytic streptococci and atrophic arthritis is, according to Dawson, Olmstead and Jost,¹⁷⁷ provided by a comparative study of precipitins and agglutinins. It was found that there was close approximation, but not absolute agreement, in the capacity of the serums of 71 patients who had atrophic arthritis to agglutinate strains of hemolytic streptococci and to precipitate various group-specific fractions of this organism. These findings suggest that agglutination tests represent a true immunologic reaction, but both agglutinin and precipitin reactions are group-specific and not specific for any particular strain. Whether hemolytic streptococci play a primary or secondary etiologic rôle cannot be concluded.

Discussing the reliability of such indirect evidence, Dawson¹⁸⁰ admitted that cutaneous reactions in his cases have been variable and difficult to interpret. No correlation was found by him between the degree of cutaneous reactivity and the clinical condition of the patient. Cox and Hill¹⁶⁰ found no apparent relationship between variations in the patient's clinical course and his agglutination titers, or between the latter and cutaneous reactions. Cecil's hemolytic streptococcus AB13, however, had greater serologic selectivity for atrophic arthritis than for any other disease-group studied, and the high percentage of serums which contained agglutinins to this strain could not be accounted for on the basis of previous artificial immunization or on that of previous or concomitant streptococcal infections. Cox and Hill concluded that agglutination to this strain has a definite but limited use as a diagnostic aid. Difficulties in interpretation of cutaneous tests were further stressed by Jones and Mote,¹⁸¹ who noted certain reactions attributable not to the streptococci but to animal proteins injected therewith.

More direct evidence of infection has been sought by others. Blair and Hallman¹⁸² made 57 cultures of synovial fluid and of tissue derived from patients who had atrophic arthritis and 175 cultures from patients who had other types of arthritis. Of the former 75 per cent, of the latter 81 per cent, remained sterile. A variety of organisms was found in the remaining cultures, to none of which etiologic significance was attached. Shapiro¹⁴⁸

found no organisms in blood cultures of 20 patients who had atrophic arthritis or in blood cultures of 30 patients who had rheumatic fever

The antihemolysin titer was found by Griffiths¹⁰⁶ to be definitely high in the majority of cases of infective arthritis and spondylitis ankylopoietica (atrophic spondylitis). According to Boys, Gunn and Lang¹⁸³ the blood of patients who had active atrophic arthritis (also that of patients who had mixed arthritis, streptococcal septicemia or certain non-streptococcal infections) contained more bacteriolysins to Clawson's strain of *Streptococcus viridans*, than that of normal controls. The blood of patients who were recovering from atrophic arthritis, or who had hypertrophic arthritis, was no more bactericidal than was that of controls.

The conclusion of most of those who uphold the theory of infection is that atrophic arthritis is most likely an infectious disease although final proof thereof is lacking. Thus they can sympathize with Key in the recital of his "personal futile attempts to prove the infectious origin of chronic arthritis"¹⁸⁴. From a multitude of cultural studies on blood synovial membrane and fluid, and on experimental arthritis he concluded that chronic arthritis of human beings is probably not caused by streptococci, staphylococci or diphtheroid organisms. Nevertheless atrophic arthritis presents many characteristics which are most satisfactorily explained on the basis of infection of low grade. Unable to discover more direct evidence in support of this theory, workers are now vigorously seeking indirect evidence in the form of skin tests and various immunologic reactions. The value of such evidence is at present impossible to measure, and the current favorite idea that the hemolytic streptococcus is the cause of the disease is built almost entirely on such indirect evidence. The idea of bacterial allergy is attractive because it seems to explain certain cultural and biologic diversities otherwise impossible to harmonize but it should by no means be accepted as an established fact. Vigorous objections to it are being registered and the value of such evidence as cutaneous sensitivity is sharply contradicted by several investigators. Thus from their skin tests on 34 patients who had arthritis, using a large number of autogenous strains and controls, Short, Dienes and Bauer¹⁸⁵ found no allergy of the arthritic patient comparable to that in cases of tuberculosis or in certain other chronic infectious diseases. Skin tests, without using several subjects as controls, are without significance. Even so variations in cutaneous reactions may be explained by differing irritability of the patients' skins, natural toxicity of the bacterial species, or possibly by sensitization to certain bacterial groups.

Wolf¹⁸⁶ listed several objections to the theory of bacterial allergy and concluded "It seems as though the whole theory of allergy has been introduced as the result of a desire to explain something which it would be far more satisfactory to describe. The conception of allergy does not explain rheumatic arthritic manifestations in general. It does not help us in therapeutics. It really only complicates the problem. The whole theory itself is vague and not clear enough to be used to clear up other problems."

[Bray¹⁸⁷ has tried to describe the so-called allergic joint and has given Pavist's (1933) classification of allergic arthropathy as follows (1) that of serum origin, (2) that of non-serum origin (a) acute forms simulating acute articular rheumatism, (b) allergic hydrarthrosis, either intermittent or chronic, (c) chronic rheumatism of allergic origin. Bray added that there is an entire lack of any convincing evidence that the so-called allergic muscular pains in the limbs of children are rheumatic in origin, for among 2000 children attending his asthma clinic, and a similar number attending the rheumatic clinic, there were only two children who gave distinct evidence of both diatheses. With the ideas quoted above from Wolf, Freeman¹⁸⁸ apparently was in complete agreement. All who would connect the terms "allergy" and "hypersensitiveness" with chronic rheumatism and arthritis should read his recent discussion thereon. According to him, the use of dermal reactions in rheumatism affords little or no assistance in settling the question of allergy. In the first place, the reactions are practically never similar to those seen in true allergic diseases. He concluded that a "fog of research" blankets the whole subject of allergy in rheumatism. "We are working in a fog and have as yet no clear vision. The word allergy is, to my mind, not a gleam of sunshine breaking through, but an extra wisp of fog"—Ed.]

Factor of circulatory disturbance. In many cases there are obvious alterations in the general blood flow—low blood pressure, cold, clammy extremities, and lowered cutaneous temperature. Some investigators, chiefly Pemberton, have laid considerable stress on such alterations as probably being of major etiologic importance. The exact nature and reason for them has not been fully determined. Kovacs^{189, 190} Wright¹⁹¹ and Hench¹⁹² have agreed that they do not represent derangements of large vessels. Many workers consider them attributable to capillary vasoconstriction. Thus, Kovacs found small, constricted capillaries in 53 per cent of cases, a slow blood flow in 65 per cent, and a decreased number of capillaries in nail beds peripheral to swollen joints in cases of atrophic arthritis. Hench was unable to find consistent alterations—some patients exhibit vasomotor alterations long before, others not until long after, the onset of arthritis, and still others not at all. Capillaries are more often dilated with a sluggish flow than constricted. After sympathectomy, with improved arterial and arteriolar circulation, capillaries of arthritic patients are not more, but less, dilated, however, the flow within them is faster. Since such circulatory alterations are so inconsistently present they must represent, according to Hench, not the cause of the disease, not even an essential part of the disease, but "a complication appearing at varying times and in varying degrees as the sympathetic nervous system is perhaps variously affected by the toxins of the disease." Wright, Kovacs and Hench agreed that capillary alterations are probably not an etiologic, but may be a definite aggravating factor, worthy of correction.

Arteriosclerotic changes were roentgenographically evident in the examination of 38 per cent of 90 patients studied by Nissen and Spencer¹⁹³. Many were less than 40 years of age and of these, 27 per cent were so affected. No definite relationship was found between the sclerosis on the one hand and the hypertension or the cardiorenal abnormalities on the other

Of 72 cases of hypertrophic arthritis, in 78 per cent arteriosclerosis was present 7 per cent of the patients were below the age of 40 years The writers could not conclude whether these findings were coincidental, or of etiologic significance

[No figures are given on the incidence of sclerosis in non-articular disease affecting patients of similar age groups, and no correlation is established between the anatomic situation of the sclerosis and that of the arthritis—Ed]

Factor of altered metabolism Different things are meant by different people when they use the term "altered metabolism" Varied is the evidence pointed out as indicating the presence of altered metabolism, and the representations made in favor of the theory of disturbed metabolism are no more, indeed less, definite than those in behalf of the theory of infection Fletcher is of the belief that the value of Pemberton's low-calorie, low-carbohydrate diet lies not so much in the curtailment of the latter as in the fact that such a diet is high in vitamins, especially vitamin B, and that vitamins act more effectively when ingested with a ration low in carbohydrate With this idea Pemberton, Peirce and Bach¹⁰⁴ expressed disagreement Patients who received a low-carbohydrate, very low-vitamin diet improved as well as those who received a low-carbohydrate, high-vitamin diet

Patients who have atrophic or hypertrophic arthritis do not tend to follow a diet essentially different from the normal in total calories or in relative amounts of proteins, fats and carbohydrates, according to Sladen, Ensign and McColl¹⁰⁵ However, on close analysis many reveal a hidden dietary error—a tendency to choose carbohydrate foods of small bulk and containing small amounts of minerals and vitamins Correction in the kind, not in the amount, of carbohydrates is in order

The well known ideas of Pemberton and his colleagues on the metabolic and nutritional aspects of the disease have been carefully reviewed again^{106, 100} Apparent alterations in sugar tolerance and in metabolic rates do not necessarily indicate pancreatic or thyroid deficiency but are probably dependent on the curtailment of blood flow to various tissues, especially to muscles The sugar tolerance was found by Nissen and Spencer¹⁰⁷ to be normal in 43 per cent and abnormal in 57 per cent of a group of 222 cases of arthritis, represented by patients, 82 of whom had atrophic arthritis 62 hypertrophic arthritis, and the remainder, arthritis of other types Correlation was not found between the sugar tolerance on the one hand and on the other the age or sex of the patient, the duration or activity of the arthritis, or the presence of foci of infection, of hypertension or of arteriosclerosis An abnormal tolerance did not necessarily become normal when the disease became inactive Nissen and Spencer queried whether the etiology of arthritis might lie in disturbed function of the pancreas, liver, suprarenal gland or pituitary body, such that the autonomic control of the body is affected without a diabetic syndrome being present

An undefined type of food deficiency was suspected as the cause of the disease by Wright,¹⁵⁰ who particularly prescribed whole wheat flour instead of white flour, and by Burnett and Ober¹⁵⁴. According to the latter, the deficiency does not occur from lack of a complete diet but from incomplete digestion and absorption of food, leading to failure of nutrient substances to construct or preserve normal bone and cartilage. Contrary to the belief of most investigators, that arthritic patients tend to exhibit definite delays in passage of a meal, Burnett and Ober expressed the belief that such a patient tends to hurry along a meal, an index of incomplete digestion and absorption. The majority of patients eat too much fat or fruit and not enough vegetables. Rather than favoring more roughage or a more rapid emptying time of the bowel the authors named favored slowing down the passage of intestinal content to a normal rate to permit anabolic nutrition.

[This entire discussion is highly theoretical. No proof is offered for statements made—Ed.]

Snyder, Traeger, Fineman and Zoll¹⁰⁸ adopted the opposite and more common view that intestinal, particularly colonic, stasis is present, and that this is exhibited by roentgenograms of redundant, atonic, dilated colons and by certain symptoms of dyspepsia. With this view Hartsock¹⁰⁹ expressed agreement.

[Objections to this viewpoint are contained in last year's review—Ed.]

The idea of the overproduction by the arthritic patient of an acid-ash from foods rich in proteins and carbohydrates has been advanced again,²⁰⁰ but Boyd²⁰¹ investigating the chemistry of urine and sweat of rheumatic patients could not conclude that the beneficial effects of heat were attributable to the elimination of acid constituents. The induced sweat of arthritic patients was chemically the same as that of normal persons.

A revival of sulphur therapy is being attempted as the result of Cawadias' theory (1927) that the cells of an arthritic patient have lost the ability to retain sulphur. Sullivan and Hess,²⁰² and Sullivan²⁰³ expressed the belief that the cystine content of the finger nails of arthritic patients of the "infective" or "mixed types" is definitely low, an indication of disturbed metabolism of sulphur. The cystine content of the nails of 103 arthritic patients averaged 9.8 per cent (7.2 to 13.1 per cent) as compared to an average of 11.7 per cent (10.2 to 13 per cent) in the nails of 30 normal persons. According to Sullivan and Hess, the body uses compounds of sulphur, cystine, cysteine and glutathione to render injurious material innocuous, a detoxication process. The low cystine content of nails may imply a factor of abnormal intoxication depleting their content of sulphur. Among 25 patients who had atrophic arthritis, Woldenberg²⁰⁴ found even lower values for cystine in nails (6.5 to 9.8 per cent, normal values presumably 12 to 12.5 per cent). However, by Senturia²⁰⁵ no variations from the normal glutathione content of blood (30 to 40 mg per 100 c.c.) were

found in the blood of 18 patients who had atrophic arthritis, nor in the blood of 27 patients who had hypertrophic arthritis, nor in that of eight who had periartthritis

Factor of endocrine relationships A commonly seen but infrequently discussed phenomenon of the arthritic patient was considered by Rugh²⁰⁶ the exacerbation of arthritis in the course of menstruation. Recalling the work of Macht, Rugh suggested that the menotoxin may be responsible. Aside from the conjectures of Nissen and Spencer,¹⁹⁷ and of Walker,¹⁷⁴ noted in the foregoing, and the statements by Pemberton and Bach¹⁶⁶ and by Ober¹⁵³ that lowered metabolic rates are frequently seen, no other data on endocrine abnormalities were forthcoming.

Conclusions on etiology and pathogenesis From this mass of confusing, sometimes conflicting, data one cannot as yet form any conclusive ideas on the etiology and pathogenesis of the disease. It is obvious that no evidence has been brought forth to change the statement of the American Committee for the Control of Rheumatism, that to date no one etiologic factor, no single infection, dietary abnormality or metabolic derangement has been conclusively shown to be the prime cause of the disease.

Treatment **General remarks** The need for a broad approach to the problem of treatment is obvious from the foregoing and was stressed by Irons,^{207, 208} Cecil,^{165, 175, 209} Pemberton and Bach,¹⁶⁶ Haden,¹⁴⁵ Archer,¹⁴⁶ Holbrook and Hill²¹⁰ and Holbrook¹⁵⁹. One must initiate a therapeutic program with an open mind, without prejudice against the theories of others, because any program of treatment based on one theory or on one causative factor will fail in clinical use. A physician must not concentrate on only one form of treatment or he will become a faddist. In selecting his physician a patient probably will do best by choosing a well-rounded internist. There is no one specific, no one standard form of treatment. Individualized, not routine, treatment of each patient is required, and the patient, not just the disease, must be vigorously studied and cared for. Because of the obvious importance of interrelated factors, correction of whatever abnormalities the patient presents is necessary.

[One gladly accepts the choice of a well-rounded internist if he be really interested in the disease. Too often "the well-rounded internist" is conspicuous for his lack of interest in arthritis and by his failure to familiarize himself with the nature of the disease and its victim. Many indulge in half-baked ideas and one-sided methods of treatment, accepting too readily the dicta of faddists. It seems obvious that, in spite of the absence of any specific treatment, best results will be obtained by him who has a broad experience with the disease and who, whether he calls himself a general practitioner, an internist, or even a "rheumatism specialist," has vital interest in the disease. To some extent official medicine in this country has been inclined to oppose the development of arthritic clinics and special institutions for the care of arthritic patients. European governments are frankly partial to such institutions. Certainly therefrom should accrue to the army of arthritic sufferers benefits similar to those which have been derived in the field of tuberculosis and heart disease—Ed.]

At first glance it would seem that treatment of the disease varies markedly in different clinics in one place removal of foci seems to be stressed, in another, postural care, in still another, dietary measures, in others, climatic care, sulphur or gold therapy, sympathectomy, and so on. As a matter of fact most physicians treat patients in much the same way although their writings may be calculated to emphasize some particular idea on treatment or cause. Cecil questioned 15 colleagues in various parts of the country as to their favorite therapy. Replies indicated that rest, removal of foci, physiotherapy and climate were favored, foreign protein, transfusions of blood, drugs and intestinal hygiene, and fever therapy ranked low in their estimate. A diet low in carbohydrate and a streptococcal vaccine won moderate recognition. Controlled experiments with various types of therapy were performed by Holbrook and Hill. Of 100 patients, each was subjected to one of the following: removal of foci, transfusions, administration of vaccine, or heliotherapy, and each was observed for from months to years. Results emphasized the non-specificity of any one measure. In consequence, a coordinated program of those measures found by experience to be most useful is essential. It is suggested that many measures obviously of slight or of questionable value should be discarded and the patient and his physician concentrate their energies and finances on measures of proved worth.

Foci of infection and their removal. Infection in foci may not precede nor be the cause of the disease but may rather be the result of the disease. As a result of basic, general, nutritional and metabolic derangements, producing localized alterations in nutrition, they may appear more frequently after the disease has started. Ducker²¹¹ expressed approval of this viewpoint, put forward by Pemberton, and has noted the tendency for successive foci to develop after the original focus has been removed. Thus, a tooth may become infected as the result of disturbed nutrition incident to arthritis.

Foci of infection were found equally present (17 per cent) in cases of both types of arthritis (3004 of atrophic arthritis, 1335 of hypertrophic arthritis) studied by Steindler²¹². Of those cases of atrophic arthritis and of hypertrophic arthritis in which focal infection was present, the tonsils were infected in 55 per cent and 64 per cent respectively, teeth in 17 per cent and 23 per cent, sinuses in 46 per cent and 57 per cent, the biliary tract in 1.5 per cent and 7 per cent, and the genito-urinary tract in 6 per cent and 5 per cent. Striking immediate improvement from removal of foci was noted in 35 per cent of cases of atrophic arthritis and in 20 per cent of cases of hypertrophic arthritis. Lasting benefits were obtained, however, in only 15 per cent of cases of atrophic arthritis and in 8 per cent of cases of hypertrophic arthritis. To Key²¹³ it seemed strange that Steindler found foci of infection in only 17 per cent of cases of both types. It has been said that almost no one reaches adult life with normal tonsils and teeth. The effect of removal of foci in these cases was not impressive—many more

than 35 per cent of patients are benefited by other measures or get well without therapy

It is erroneous to believe that tonsillectomy can adequately remove a focus of infection. Infection is not localized in the tonsils but is spread widely over adjacent nasopharyngeal tissue which may appear normal, according to Solis-Cohen.²¹⁴ From 95 per cent of normal appearing nasopharynges he got positive cultures for infecting organisms, often the same organisms as those found in removed tonsils. The terms "removal," "eradication" or "elimination" of foci of infection are only relative, and to counteract the toxins elaborated by the irremovable infections, stimulation of antibodies and of bactericidins is necessary. This is done, as previously outlined, by Solis-Cohen's method of vaccine therapy based on pathogen-selection (the use in his vaccine only of organisms which grow in, and are not killed by, the patient's own serum). The dangers of silent sinusitis have been discussed again by Snyder, Fineman and Traeger,²¹⁵ the fourth time a report on this same series of cases has been published.

Early eradication of foci has been to Cecil,^{175, 209} and to many others, the keystone of the arch of treatment. To Cecil removal of infected tonsils is the most important, the care of infected sinuses and teeth next in value. Even tonsils which arouse suspicion should be removed early. Devitalized teeth are removed only when periapical infection is visible, and in the treatment of sinusitis Cecil wrote that he followed the advice of a "none too radical laryngologist." With this plan, Archer,¹⁴⁶ Pemberton and Baeh,¹⁶⁶ Clinie,⁵ and Sprunt¹⁷⁶ expressed agreement. Foci of infection should be removed early, the sooner the better, and one should not "wait till the patient is stronger." Removal of a focus after it has spent its force cannot repair a joint and not only is of no value but may be dangerous. But foci must be removed "intelligently"²⁰⁷ and "at the proper time."¹⁴⁵ Holbrook¹⁵⁰ expressed the belief that early removal of foci is of much greater value in febrile cases (infectious or "b" group), with a subacute onset, than in cases of the more chronic and insidious type. Removal of foci in the latter group may be disastrous unless proper precautions (a building-up process, measures against fatigue, exhaustion, constipation and malnutrition, preliminary transfusion) are taken. To R and J Kovacs¹⁴⁰ results of removal of foci have been disappointing.

Vaccines. From published reports it is very difficult, if not impossible, to determine the value of vaccines. They are prepared and given in so many different ways, almost always in conjunction with other therapy, and rarely are results with a control series given. Statements relative to vaccines must be considered as statements of impressions, not as declarations of indisputable facts, even though, often, they are made after long experience. The situation is difficult if not impossible to remedy, for few physicians or patients have sufficient faith to rely on vaccines only, and the natural course of the disease is varied by seasonal and other remissions. The majority of investigators now believe that they are attempting desensiti-

zation, not immunization, and therefore favor very small doses, which do not produce significant reactions. Systemic reactions are to be avoided. Minor local and focal reactions may be permissible if followed by a significant period of euphoria (improvement reaction). Some workers even avoid all focal reactions and seek to use the smallest dose which gives relief without reaction.²¹⁶

When vaccines are given, they should be administered for long periods "several months at least,"²⁰⁹ "for 6 to 12 months,"²¹⁷ "for 6 months to 2 years."²¹⁸ Results should not be evaluated until after three or four years,¹⁴⁸ to determine whether a temporary or a lasting effect is obtained. Cecil^{165, 175, 209} expressed himself as favoring administration of his stock, hemolytic streptococcal vaccine intravenously or subcutaneously, in many cases he has obtained gratifying results. Of 35 patients treated by Marvin²¹⁹ with Cecil's vaccine, five were markedly benefited, nine moderately improved, 10 slightly improved, and 11 not improved. Discouraged by previous subcutaneous or intramuscular administration, he gave the vaccine intravenously. No control series was reported. With Cecil's vaccine given intravenously, Higgins'³⁰ results have been far from satisfactory but there was an occasional brilliant result.

Crowe's polyvalent vaccine (staphylococci, streptococci) was favored by Carlson,²²⁰ Nutter and Watson,²²¹ and Nuttall,²²² Wright,¹⁵⁰ and Adamson.⁶ Of 137 patients who had chronic (undifferentiated) arthritis, treated by Nutter, 65 became symptom-free and remained so for at least five months.

[No other statistical results were given—Ed.]

Bacterial filtrates, such as are used by Small, were favored by Cohen²²³ and by Lawler.¹¹⁴ The pathogen-selective method of preparing autogenous vaccines was favored by Solis-Cohen,²¹⁴ and by Murphy,²¹⁷ who used vaccines in addition to other measures. Cutter's diluted cold vaccine (staphylococci, streptococci, pneumococci, *Micrococcus catarrhals*, Friedlander's bacillus, and influenzal bacillus) was used with good results by Sherwood¹⁴¹ in 220 cases of chronic arthritis of various types. "Usually after 12 to 20 treatments the patient will be much relieved."

[Presumably no other treatment was given, but no controls were studied—Ed.]

Of 28 patients treated by Wainwright¹⁷⁹ with vaccines prepared from strains of microorganisms to which patients were skin-sensitive, 75 per cent were benefited. Five of eight bed-ridden patients were able to be about. Subsequent skin tests gave evidence of less sensitivity or became negative, the patients' agglutinins increased and sedimentation rates diminished. Similar vaccines were used by Rogers²²⁴ in 15 cases. In mild cases improvement was marked, in more severe cases less improvement was noted. Anaerobic, as well as aerobic organisms must be included to obtain results. Although one would prefer to use strains presumably responsible for the patient's sensitization, the determination of such strains was, to Hitch-

cock,¹⁷⁸ a formidable matter, consequently stock strains of hemolytic streptococci were used

The methods used in preparation of these various vaccines are to a large extent based on false premises and on assumptions that are not susceptible of proof, according to Short, Dienes and Bauer,¹⁸⁵ who pointed out the inadequacies of skin tests, complement fixation tests, and the pathogen-selective method. Skin tests do not provide a sound method for determining a patient's susceptibility to autogenous organisms. None of the different methods recommended for the selection of strains from which to make specific vaccines has a solid theoretical or experimental foundation. Such results as are obtained are those of the non-specific effect of the vaccines. Buckley^{30, 161} agreed that "specific vaccines" are probably neither specific nor essential. In his hands, Pondorff's cutivaccine has given variable but interesting results. Vaccines have a definite but distinctly limited place in the scheme of therapy according to Holbrook,¹⁵⁹ Irons,²⁰⁷ and Pemberton and Bach.¹⁶⁶ Used alone, they rarely cure patients. Various preparations were administered variously by Holbrook¹⁵⁹ and Holbrook and Hill²¹⁰, only occasionally was improvement noted that was not easily accounted for otherwise. Minute doses of vaccine administered intravenously gave the most favorable results. More cripples than cures may result from indiscriminate and injudicious use of vaccines^{30, 159}. Unsatisfactory results with Cecil's and with Clawson and Wetherby's vaccine were obtained by Archer¹⁴⁶ who expressed the belief that such results as are obtained may be largely psychogenic. No striking results were noted by Shapiro¹⁴⁸. In the study by Cox and Hill,¹⁶⁰ vaccine therapy was not followed by correlated changes in agglutinins.

Regarding the intestines as a focus of infection, and considering the value of "intestinal vaccines," Buckley¹⁶¹ expressed the opinion that the possibility of the infecting organism becoming an inhabitant of the bowel can be ignored. "There is sufficient evidence that bacteria do not normally enter the circulation from this source, and the toxins, if absorbed, are probably greatly modified if not destroyed by passing through the lines of defence."

Foreign proteins. These substances seem useful to some investigators^{176, 225}. Brooks¹⁴² continued to favor the use of his hemoprotein, given without reactions, in conjunction with other measures. Lawler¹¹⁴ used typhoid bacilli as the most available means of producing fever in 36 cases of arthritis of various types. Improvement was generally only temporary. Wetherby¹⁴⁷ considered typhoid vaccine of little value.

Diet. Attention to the ideas concerning the factor of nutrition and metabolic derangements will explain the supposed rationale of the various popular "rheumatism diets". The same familiar diets or slight modifications thereof are again candidates for approval: the low-carbohydrate, low-calorie diet, the high-vitamin, low-carbohydrate diet²²², the high-calorie, high-vitamin diet^{140, 210}, the individualized diet. To his familiar arguments

in favor of a low-calorie, low-carbohydrate diet Pemberton and his colleagues,^{160, 164} added another, namely, that such a diet exerts a definite dehydrating effect on body tissues in both types of arthritis¹⁶⁰ The loss is in pathologic, not in physiologic fluid Definite reduction in periarticular swelling and articular pain are realized

[This interesting suggestion needs further confirmation The water balance studies in these experiments were approximate, not absolutely controlled—Ed]

Various modifications of the diet just mentioned were favored Avoidance of free sugar by Douthwaite,¹²¹ a starch-free diet and administration of pancreatin by Walker¹⁷⁴

[Has pancreatin ever been shown to have any provable physiologic effect? We do not believe so—Ed]

Pemberton's diet seemed of little benefit to Wetherby's patients¹⁴⁷ Other investigators still restricted purine foods "because the blood uric acid is often high"²²⁶

[We disagree with this, the blood uric acid is rarely high and restrictions of protein generally are not indicated—Ed]

As previously noted a hidden dietary error was corrected by Sladen, Ensign and McColl¹⁹⁵ by rearranging the kinds, not the amounts, of carbohydrates ingested

The majority of investigators expressed the belief that no one diet is of value Constipation, inanition and obesity are all to be avoided or corrected by a diet arranged for the individual patient The details of their diet for anabolic nutrition were outlined by Burnett and Ober¹⁵⁴

Additional intestinal therapy Colonic irrigations were recommended by some,²²² avoided by others^{175, 210} They may be fatiguing if given too often and should rarely be given to people who are on "a low nutritional equilibrium"¹⁶⁶ To control intestinal elimination, mineral oil, agar-agar, oil retention enemas, glycerine suppositories, and abdominal exercises were recommended by some,²¹⁰ but were frowned on by Burnett and Ober¹⁵⁴

Blood transfusions Transfusions of 250 to 500 c.c. of blood may be indicated in cases in which there is severe anemia^{140, 166} They may be helpful in subacute and early, chronic, febrile cases but are of little value in the very chronic, afebrile cases in which pathologic changes are advanced^{159, 210}

Medicines Many medicinal preparations are used generally as adjuncts to more important measures iron, arsenic, liver extract various analgesic substances, cod liver oil, viosterol, haliver oil, potassium iodide, thyroid extract, wheat germ, yeast, nitrites for vasodilation in selected cases, strychnine or nux vomica for fatigue Cecil¹⁷⁵ agreed with Haden that neoarsphenamine gives good results occasionally, but Moltke¹⁶³ saw no rationale therefor Wheeldon²²⁷ wrote that he used calcium ortho-iodoxybenzoate "to improve peripheral circulation"

Preparations of gold Various preparations of gold (solganol, allo-

chrysin, myocrisin) are being used in continental Europe. Further experience with allochrysin (sodium aurothio-propanol sulphonate) were reported by Forestier,²²⁸ who in five years has treated therewith 500 cases of atrophic arthritis, 70 to 80 per cent responded well. In 50 per cent of early cases, and in from 20 to 30 per cent of those in which the arthritis was of more than two years' duration, permanent cure was reported after two to five series of injections. "Myocrisin" is injected weekly, the individual dose is 0.1 to 0.2 gm and the total dose 1.5 to 2.0 gm in one series. Untoward reactions may be noted in the skin and in the respiratory, alimentary, nervous, and urinary systems. Nephritis has been produced in man and in animals, the gold is excreted mainly through the kidneys. Jaundice, leukopenia, or febrile reactions may be observed. Slot and Deville¹¹⁵ treated 14 patients with solganol and improvement was "great." Buckley used allochrysin "in a certain number of cases with some promising results." The sulphur therein may act synergically with the gold.¹⁰¹ Cecil's¹⁷³ results with salts of gold were "not striking."

Compounds of sulphur. A renaissance of sulphur therapy is current. Weekly or biweekly injections of sulphur are generally given intramuscularly, 20 mg in oil or 5 mg intravenously. After 10 or 12 doses have been given, a rest of 10 days is permitted. Two or three courses are generally prescribed. Untoward reactions, aside from occasional, small, cutaneous sloughs or febrile reactions, were not reported, and presumably there are no contraindications. Senturia²²⁰ used sulphur-diasporal in the treatment of 55 patients who had atrophic and hypertrophic arthritis and gave it also to five patients who had fibrositis. Of this total, 75 per cent were "improved", 31 per cent markedly so. From 10 to 76 injections were given. Four of seven patients treated by Sullivan and Hess²⁰³ were "appreciably" or "markedly" improved. Later all of six patients were improved.²⁰³

[The same patients?—Ed.]

Sullivan²⁰³ noted definite increases in the cystine content of the nails during therapy. Of 100 patients treated by Woldenberg²⁰⁴ the majority became free of pain after five or six injections. However, all received a variety of other forms of treatment. In seven cases, Argy²³⁰ noted no improvement until after five injections, thereafter, in six improvement was noted. It is suggested that better results are to be expected if the cystine content of the nails is low before treatment. To Cecil,¹⁷⁵ however, injections of sulphur have been disappointing.

[In none of these series, practically all of but a few cases, have control studies been carried out. In the one fairly large series many other forms of treatment were used in addition to sulphur. It seems well to wait for controlled studies before considering that treatment with sulphur deserves to be resurrected from limbo simply because "new" colloidal preparations are available. Our brief note in last year's review, that such therapy was being revived, has already been used in advertising matter praising treatment with sulphur, although not the faintest approval was voiced by us.—Ed.]

Histamine and choline The recent use of histamine for rheumatic diseases was initiated by Deutsch (1931). The claims for such treatment in Germany seem extravagant. From European literature Kling²³¹ collected data on 554 cases of arthritis, neuritis or myalgia so treated by various physicians. Of 316 patients who had myalgia (myositis), 96 per cent were "improved or cured." Of 85 patients who had arthritis, more than 90 per cent were improved. Histamine, given by cataphoresis, ionization, in ointments during massage, or by the scratch method presumably produces capillary and arteriolar dilatation, correcting an altered peripheral circulation. Kling's results^{231, 232} were less striking. Of 32 cases of myositis, in 75 per cent he had a favorable result. Of 14 patients who had hypertrophic arthritis, eight were helped. No conclusions were reached as to results in 24 other cases of arthritis. The use of histamine, byunction or ionization, was praised by Mackenna,²³³ for fibrositis and chronic villous arthritis. It does not change the course of the latter but relieves symptoms for variable periods. With its use, it is "possible completely to cure fibrositis and neuritis." Histamine and thiohistamine are particularly useful in the treatment of periarticular arthritis accompanied by cold, cyanotic fingers, according to Shanson and Eastwood¹¹⁶ who favored intramuscular injections rather than ionization. The benefits of foreign protein therapy, according to Buckley,³⁹ may be attributable to liberation thereby of a histamine-like substance.

[It is to be noted that here again the number of patients treated was generally small, no real control studies were instituted, a confused nomenclature was used, data on the type, severity and duration of the arthritis were almost wholly lacking, and certain of the conditions cured (for example myalgia) were of limited duration—Ed.]

In a series of papers, R and J Kovacs^{140, 234} and J Kovacs^{189, 190} gave the basis for preferring ionization with mecholol (acetyl-beta-methylcholine chloride) rather than oral, subcutaneous, or intravenous use of histamine, acetylcholine or nitrites. The general and local (vasodilating) effects of these were compared. The Kovacs contended that the action of mecholol is more lasting, less unpleasant, and more effective. Of 30 patients who had atrophic arthritis, 90 per cent were improved. Patients who had osteoarthritis were also improved but not more than with more established methods.

Climatotherapy Climate provides no panacea¹⁶⁰. However, a stay in a high, dry climate may be advantageous in some cases²⁰⁹ but not without the use of other forms of therapy^{150, 210}. In and about Tucson, Arizona very few native white people have arthritis. The incidence of the disease among local Indians is less than among those elsewhere. Many patients, unrelieved at home, obtain notable relief in Arizona "but it must be understood that without the proper routine of living (a coordinated program of therapy), arthritis even on the Tucson desert can continue as a sad and crippling disease."

Rest and movement The great value of adequate rest for the inflamed joints, and also for the fatigued body, of the arthritic patient was stressed by many "If one single remedial agent was to be chosen, rest would be the one selected"¹⁵¹ "As in tuberculosis, so in arthritis, rest is the key-stone of the arch"¹⁶⁶ "Motto—no weight bearing on swollen joints"²³⁵ "Rest till signs of inflammation have subsided"²³⁶ As the acute blends into the subacute and chronic stage, rest may be sharply overdone The recumbent patient who has arthritis must not be taught only how to lie correctly but must exercise in bed as the daily condition of the joints permits "A movement a day keeps adhesions away"²³⁵ Early motion is necessary and often too much rest is prescribed When, because of pain and stiffness the patient does not cooperate in the prevention of deformity, the way is paved for the production of arthritic derelicts "The price of comfort is crippling"⁵ Hench and Meyerding²³⁷ have presented examples of these arthritic derelicts—patients who have allowed themselves, or who have been permitted, to become human pretzels from grievous deformities generally induced by rest, often deliberately prescribed A detailed and diagrammatic synopsis of methods of prevention of deformity available for use by physicians in the patient's home was given by Hench and Meyerding Swaim²³⁸ has outlined again the tenets of the Boston school concerning postural and other exercises, and measures for the prevention of deformities

Physical therapy and manipulation As usual, each form of physical therapy has its advocates The value and indications thereof are too well-known to need review here, but the merits of many are cited various forms of heat,^{239, 240} paraffin baths,²⁴¹ infra-red and diathermy,²⁴² effervescing immersion baths,²⁴³ contrast baths,²⁴⁴ fangothrapy,²⁴⁵ hydrotherapy,^{246 247} applications of cold,²⁴⁸ manipulation^{249, 250, 251, 252, 253, 254} The teaching of physical therapy to undergraduates and to the general practitioner who needs to know much more about it was discussed by Cutter and Coulter²⁵⁵ and by Kovacs²⁵⁶ A central registry can inform any physician of the nearest physiotherapists²⁵⁷

Fever therapy, artificial hyperpyrexia This is the newest form of physical therapy Experience with it in treatment of atrophic arthritis has shown that results therein are not nearly as good as they are in gonorrheal arthritis The first dozen reports were analyzed in last year's review Using diathermy-hyperpyrexia (five hours at an oral temperature of 104° F, one to five sessions) in the treatment of 12 patients, Nicholls, Hansson and Stamsby²⁵⁸ noted cures or marked relief of none, moderate relief of 25 per cent and little or no relief of 75 per cent They considered it a trying ordeal for the patient and did not feel justified in continuing its use Osborne and Markson's third and fourth reports^{27, 359} concerned results of 188 treatments administered to 28 patients The usual course was eight treatments (each of 6 to 8 hours at an oral temperature of more than 104° F) Remissions were induced in many cases, and from 50 to 70 per cent of the patients, grouped according to severity of the disease, were

considered improved Merriman, Holmquest and Osborne²⁶⁰ recently have advocated the use of an inductotherm to decrease expense and for the sake of ease in therapy About 75 per cent of 40 patients treated by Simpson²² with radiothermy or in heated cabinets (Kettering hypertherm) were definitely improved Diathermy-hyperpyrexia was advocated by Jones²³ A safe method of producing fever, by hot baths in the patient's home, was outlined by Currence²⁶¹ Cecil¹⁷⁵ preferred injections of typhoid vaccine to fever induced by diathermy For discussions on the relative merits of various methods for producing fever, and for details on the physiologic reactions produced thereby, various new references are available^{26, 262 to 272} Hoverson²⁷⁰ has reported the case of a paretic patient who survived an uncontrollable hyperpyrexia that rose to 110.5° F Short and Bauer,²⁷¹ and Hench, Slocumb and Popp²⁷² recently have reported their results In general the effect of fever therapy in atrophic arthritis was disappointing Satisfactory remissions were occasionally induced About 25 per cent of patients noted definite improvement None were cured Hench²⁷³ also has summarized the entire national experience with fever therapy for atrophic arthritis of about 200 patients so treated less than 10 per cent became symptom-free, about 25 to 30 per cent noted some relief Results with various methods do not differ materially The choice of method resolves itself into the selection of that which is safest, least expensive and most comfortable for the patient Hench expressed his preference for humidified, heated cabinets Untoward reactions are rare when the procedure is supervised, in a hospital, by trained nurse-technicians and an attending physician Severe reactions, even death, are occasionally encountered The Council on Physical Therapy of the American Medical Association recently²⁸ reported on the results obtained by 4809 patients, who had different diseases, treated by various physicians, with different forms of fever therapy Twenty-nine deaths were noted, many of them among neurosyphilitic patients

[With care in selection of patients, and with skilled management, the procedure is essentially safe—Ed]

Surgical Procedures Synovectomy Occasionally synovectomy is indicated for an old, boggy, proliferative, inflammatory process in a knee that is unresponsive to conservative therapy, and if the condition is not accompanied by much arthritic activity in other joints²⁷⁴ Busby²⁷⁵ expressed the belief that synovectomy is at times necessary to correct an otherwise uncorrectable articular focus of streptococci

Sympathectomy This procedure was initiated in selected cases of arthritis by Rowntree and Adson (1927) and its physiologic rationale was further outlined by Hench and Craig (1931) It is a method of value in certain cases²⁷⁶ In Young's²⁷⁷ experience "several cases of distressing and seriously disabling chronic polyarthritis of the hip, knee, and ankle have been relieved almost beyond belief by lumbar sympathectomy" In treat-

nt of a child who had early swelling and deformity of the legs, resection of lumbar trunks by Robertson²⁷⁸ "caused or immediately preceded a rapid complete return to normal" In another "more advanced and severe," after operation, "pain and the vascular condition of the lower limbs were very markedly improved The patient's comfort was greater but that was the net result" Robertson felt that these "results were striking and could encourage one to operate in these cases at as early a stage as they can be found" Unilateral cervicothoracic sympathectomy was performed by Sford²⁷⁹ on an elderly woman who had marked arthritis of the joints of the right arm "Complete pain relief and a considerable increase in the use of the hand and arm" were the results

[Some question the rationale of sympathectomy in a disease presumably infectious Those who initiated and advanced the trial use of this procedure for atrophic arthritis were not proposing a "specific measure" for a disease of supposed neurovascular origin They were advocating a measure designed to counteract a "complication" variably present in differing degrees in a disease which might well be infectious The complication—a vasomotor disturbance presumably responsible for inadequate blood supply to affected and already seriously embarrassed extremities—occasionally be of sufficient severity to warrant attempts for its correction in the most complete and lasting way possible—sympathectomy Sympathectomy is therefore regarded by its proponents as a sort of continuous infusion of the patient's own blood in behalf of just one part of his body—the peripheral portions of his cold, clammy arthritic extremities If thereby the blood flow thereto is significantly augmented (as indirect, not direct, evidence seems to suggest) and if the patient's blood still sufficiently potent in its concentration of specific and "non-specific" healing substances, good results may be obtained, analogous to repeated transfusions If such not the case the infusion via sympathectomy will be of no more value than an ordinary transfusion to a hopelessly sick or dying man The crux of the matter lies in proper selection of the patient

Since the original workers in this field are wisely postponing their final report because others have performed sympathectomy on but three or four cases, the value of sympathectomy in atrophic arthritis is not yet established—Ed]

The selection of cases for sympathectomy was again discussed by Brown, Craig and Adson²⁸⁰ Suitable are young patients who have fairly severe atrophic arthritis, especially in hands and feet, who have cold, clammy extremities and little bony change, and who are unrelieved by conservative measures A higher grade of postoperative vasodilation is obtained in the hands and feet than in less peripheral tissues Several questions are frequently asked What changes are present in excised tissues? Does the operation produce significant vasodilation? Are the postoperative changes permanent? Do ill effects eventually accrue to body tissues? Is there a possibility that sympathectomy might eventually produce neuropathic joint disease?²⁷⁴ Changes in the excised ganglia, according to Craig and Kernof (1933), were comparable to those found in ganglia removed at necropsy in patients unaffected by arthritis or derangements of the sympathetic nervous system Kuntz²⁸¹ found the same changes in ganglia removed from 19 patients who had chronic polyarthritis, but he was inclined to

emphasize their departure from normal and he disagreed with Craig and Kernohan chiefly as to the appearance of normal human ganglia

[Since what is the normal appearance of a ganglion of man has not been established, differences of opinion will arise Kuntz assumed that ganglia of normal human beings and of normal animals are identical but since this has not been established, it, like previous ideas, constitutes only an opinion One might disagree with him when he assumes that the free, intracapsular elements around ganglion cells are phagocytes rather than satellite cells of the ganglion cells At any rate, the changes observed in the ganglia in individual cases were not specific and could not be related directly to arthritis or to other diseases in question—Ed]

Although they were unable, by the injection of an opaque substance, to visualize dilatation of smaller vessels after unilateral sympathectomy of dogs (such as was demonstrated by Horton and Craig, 1930) McMaster and Roome²⁸² found an increased cutaneous temperature most marked distally on the side on which operation had been performed They, therefore, assumed that such vasodilation as occurs probably takes place in smaller arterioles and capillaries

[McMaster and Roome used a thick suspension of vermilion water color Horton and Craig used metallic mercury, a heavier substance of greater penetrability—Ed]

Studying vasomotor reactions of cats on which sympathectomy had been performed, Rosenbluth and Cannon²⁸³ suggested the presence of vasodilator centers and central tracts susceptible of direct stimulation In sympathectomized animals, dilator fibers in dorsal roots are probably efferent paths of response to stimulation of the depressor points, and also to stimulation of the vasomotor reflexes and of the dilator impulses responsible for various reactions such as a fall in blood pressure attending struggle Granting that certain permanent alterations are produced by sympathectomy in man, are they eventually harmful to various organs? In animals 22 to 42 months after operation, Clark²⁸⁴ found no gross changes which could be attributed to absence of the sympathetic system Thymus glands were infiltrated with adipose tissue There was no gross evidence of regeneration of sympathetic trunks or ganglia, and histologic studies disclosed practically no changes except for minor ones in the thyroid glands or testes These, and the studies of Brown, Craig and Adson, would lead to the conclusion that in man permanent vasodilation, but no harmful effects, are produced by sympathectomy

Splenectomy in arthritis with splenomegaly Following the example set by the admirers of Still, from time to time various names have been attached to the combination of arthritis in association with alterations in the blood picture and with involvement of one or more parts of the reticulo-endothelial system (lymph nodes, liver, spleen) The so-called Felty's syndrome is the latest such syndrome (arthritis, splenomegaly, leukopenia) Felty (1924) himself concluded that the syndrome was probably not a new disease and others have felt that it is merely another pathologic combination

of arthritis and reticulo-endothelial reaction, little different from other syndromes reported by Chauffard (1896), Still (1897) and Herringham (1909), and that a new name is therefore unnecessary. We have noted that Moltke¹⁶³ agreed with those who believe that adult or juvenile Still's disease is but atrophic arthritis with a little different physiologic response than usual. Splenectomy has been done occasionally in such cases⁴ recently by Hanrahan and Miller (1932) and lately by Craven²⁸⁵. The patient whose case was reported by Hanrahan and Miller obtained some relief for at least four months. Craven's patient obtained only transient improvement in the arthritis, leukopenia, and hepatic function. In a similar case Price and Shoenfeld²⁸⁶ considered sympathectomy, but this was precluded by fatal pericarditis. The spleen in the latter case, and in that of Craven, presented the pathologic picture of chronic infectious splenitis. Price and Schoenfeld concluded that "Felty's syndrome" is not a new disease or syndrome but merely a single, extended pathologic process.

[It should be pointed out again that the pathologic findings in these various combinations furnish considerable support for the theory of infection as a cause of atrophic arthritis—Ed.]

Thyroidectomy This has been advocated in selected cases of atrophic arthritis by Duncan (1932) and was approved by Ober¹⁵³ if definite hyperthyroidism is present.

Articular bone puncture The evidence in favor of this procedure as recommended by Mackenzie (1932, 1933) has not been impressive to his fellow-countryman, Ducker²¹¹.

[The latter, however, has not so treated any cases himself—Ed.]

Orthopedic procedures When deformity impends, it is as much the duty of the attending physician, as of his orthopedic colleague, to be familiar with simple home methods of preventing or correcting them. If deformities seem inevitable, it is imperative that the affected joints be kept in the best position for optimal function or for subsequent orthopedic procedures. These positions have again been concisely and diagrammatically outlined by Schrock,²⁸⁷ McBride²⁸⁸ and Hench and Meyerding²⁸⁷. The various corrective, non-surgical orthopedic procedures necessary for articular rehabilitation of children were surveyed by Green and Ober²⁸⁹.

Prognosis *Remissions, Spontaneous and Precipitated* The observations of Nissen and Spencer¹⁵² on the course of atrophic arthritis have been noted. Although many investigators would be inclined to agree with Archer,¹⁴⁶ that advanced atrophic arthritis seems to be incurable by the physician and that nature alone is in control of the outcome, nevertheless the majority will not accept so pessimistic a viewpoint. There is ample evidence that a coordinated program made up of those reasonable measures which an intensive study of the victim's physiologic processes will indicate, if carefully instituted and patiently persevered in, is in time followed by distinct

amelioration, and often by complete inactivity of the disease Brooks¹⁴² and others have emphasized the length of time over which it is necessary to carry on treatment to accomplish results To a large extent, the degree of recovery experienced depends on the intelligence of the patient as well as on the skill of his physician

"There is no panacea and none is needed as statistics show that a high percentage of cases properly treated recover"¹⁶⁶ The chief discontent of all is based, of course, on the fact that treatment often takes so long and requires so much of the patient's time, money and endurance before the final natural or induced remission occurs and the disease becomes finally inactive As Pern²⁸⁶ said, "Though the road may wind up hill all the way and the journey take the whole long day, the night will pass and with it its fears and dreads The dawn will break and with the dawn the mists will melt and full day will bring understanding and with it crippled joints and broken lives will belong to the night that is passed" Rather lyrical but none the less true

Since sudden remissions are not the rule, Hench²⁹⁰ was particularly interested in the precipitous remissions induced by intercurrent jaundice in 16 cases of atrophic arthritis and fibrositis In most instances the jaundice was caused by the toxic action of cinchophen but the marked, generally complete analgesia experienced with the onset of jaundice was in no way attributable to cinchophen, for patients who had simple catarrhal jaundice experienced similar relief In the majority of cases, marked reduction in swelling and marked increase in motion accompanied the more or less complete analgesia, and the rheumatic process can be said to have suddenly become inactivated The remissions lasted for variable periods, sometimes only for days or weeks, occasionally months or years Further investigations are under way to see if the obvious therapeutic implications can be realized so that one can repeat nature's miracle, and provide at will a similar beneficence by the use of some non-toxic accompaniment of jaundice effective in available concentration These observations have been confirmed by Sidel and Abrams,²⁹¹ who noted, with the onset of jaundice, abrupt termination of arthritic pain in four cases, in one of which there was also marked reduction of swelling, stiffness and redness In two instances the jaundice was of the catarrhal type, in two, it followed the use of oxyiodide (cinchophen)

HYPERTROPHIC ARTHRITIS

Incidence Recent roentgenographic and pathologic evidence (for example, Heine, 1926) indicates that hypertrophic arthritis (the clinical syndrome as contrasted with a roentgenographic alteration) is universally present among persons whose age is more than 45 or 50 years but that it is symptomatically evident in examination of only a very small proportion of its victims—probably 5 per cent It may very occasionally appear when persons are between the ages of 30 and 35 years, with other evidences of

premature senescence (early grayness of hair, early spontaneous or artificial menopause) In spite of the enormous prevalence of the disease, it is rarely dignified by studies directed primarily to it, but it is usually mentioned only in passing to emphasize some contrasting relationship to, or as a "control" for, atrophic arthritis

[American studies on the pathologic incidence of hypertrophic (degenerative) arthritis are now forthcoming Keefer and Myers (1933), Bauer and Bennett (1933) —Ed]

Symptoms and Course New data on symptomatology have not appeared In the discussion on the course of atrophic arthritis as contrasted to that of hypertrophic arthritis, observations by Nissen¹⁵¹ and Nissen and Spencer¹⁵² on the course of hypertrophic arthritis were noted In 3 per cent (one case) of 30 cases, course A (early functional restitution) developed, in 70 per cent (23 cases), course B (remissions, relapses, steady decline) developed, no cases followed course C, and 20 per cent (six cases), course D (progressive fairly rapid disability until death)

[As we noted heretofore, the idea that hypertrophic arthritis leads to death is not consistent with the facts —Ed]

Röntgenograms and Pathology No new studies were available for this review

Laboratory Data As noted previously herein, the leukocyte count is likely to be lower and the Schilling differential count to be normal in cases of hypertrophic arthritis, as contrasted to alterations in cases of atrophic arthritis^{167, 168} The cell count of synovial fluid in one case of Keefer, Myers and Holmes¹¹ was total cells per cubic millimeter, 600, polymorphonuclears 88 per cent, lymphocytes 8 per cent, monocytes 4 per cent

[A count in one case is of no significance, since so few such counts have been made, however, this case is noted —Ed]

Metabolic rates Among 21 patients who had hypertrophic arthritis of the hips, and who were seen by Kuhns,²⁹² metabolic rates were low in 18 cases

Etiology and Pathogenesis Under general remarks on the etiology of chronic arthritis were noted various ideas concerning the cause of hypertrophic arthritis Those investigators who stressed the prime importance of infection as a factor are in the minority The majority recognized tissue-age and trauma as the most obvious causal agents Few writers were satisfied to consider but one factor responsible for the disease—an interplay of abnormalities is generally incriminated (1) degenerative tissue-changes incident to age—the progressive, uncompensated catabolism of tissue-senility, (2) long continued trauma above and beyond the ability of articular tissues to repair the "microtraumatic" damage, (3) a circulatory derangement, (4) some nutritional abnormality, (5) an endocrine deficiency, or (6) the factor of infection Thus Kuhns,²⁹² from a study of 79 patients who

had hypertrophic arthritis of a hip, concluded that the disease is the product of several factors—trauma, faulty posture, disordered intestinal function, infectious and endocrine disturbances

[Some of us believe that one major cause exists, the discovery of which will result in a realignment of all other factors into their proper secondary position as precipitating or predisposing, not causal factors—Ed.]

Factor of tissue degeneration Because of the age-incidence of the disease, the general absence of the usual signs of an infectious process, the frequent association of the disease with recognized evidences of tissue senility, and particularly because of the degenerative nature of the articular pathologic change, hypertrophic arthritis is considered by most investigators to result from an "altered metabolism" [whatever that may be—Ed.] incident to age.¹⁷⁵ The theory gains some weight from studies by Bruger and Poindexter,¹⁷¹ and by Hartung, Greene and Bruger,¹⁷² on the cholesterol content of blood. There was an increase of plasma cholesterol, not explained by the fact that patients who have hypertrophic arthritis tend to be obese. The range among 50 cases was 140 to 340 mg. of cholesterol for 100 cc. of plasma. The arithmetic mean was 235 mg. (as compared to 195 mg. for the control group and 175 mg. for a group of 50 patients who had atrophic arthritis). Since similar elevations are found in diseases considered degenerative (hypertension, arteriosclerosis, diabetes), an elevation of plasma cholesterol in cases of hypertrophic arthritis suggests that this is also a degenerative disease.

Factor of trauma Higgins³⁰ and Swain¹⁷³ wrote of the importance of this factor. The importance of occupation as an inciting agent was stressed by Higgins, who stated that laundresses seem particularly prone to the development of Heberden's nodes.

Factor of circulatory alterations Pemberton's ideas on the relationship of sluggish capillary circulation and altered tissue nutrition to the causation of hypertrophic as well as of atrophic arthritis are familiar to all. Of probable etiologic importance, he felt, is this combination of circumstances—capillary constriction with sluggish flow, delay in the normal delivery of certain constituents of the blood, especially oxygen and glucose, to certain tissues, partial tissue anoxemia, further metabolic disturbances at least partly responsible for the pathologic changes in, and the symptoms of, arthritis.¹⁹⁶

Since Wollenberg (1908) launched the "circulatory theory" of arthritis deformans and showed experimentally that interference with the circulation to articular bone was followed by hypertrophy of bone (an experiment more recently repeated by Goldhaft, Wright, and Pemberton, 1930), more obvious evidence of circulatory deficiency, probably from arteriosclerosis, has been sought in cases of hypertrophic arthritis. Of 72 cases, in 78 per cent Nissen and Spencer¹⁹³ found arteriosclerosis demonstrated in

roentgenograms of various sites Of these cases, in 7 per cent the patients were less than 40 years of age

[As we noted before, anatomic correlation was not shown between the arthritis and the arteriosclerotic vessels—Ed]

Kovacs^{189, 190} found small capillaries in 28 per cent, a slow blood flow in 53 per cent of his cases of hypertrophic arthritis, with a decrease in number of capillaries near Heberden's nodes Bick²⁹³ found definite hypertension in 90 per cent and varicosities of lower extremities in 77 per cent of his cases From certain experiments and philosophic considerations, Bick has concluded that most cases of osteo-arthritis demonstrate clinical evidences of circulatory abnormalities, and that "all investigations on the mechanics of osteo-arthritis point to the peripheral vascular system as the *modus operandi* of its etiologic forces" The advent of senile involution produces a systemic passive congestion which results in failure of circulation to the cartilage, thinning, erosion and fibrillation of cartilage and hyperplastic reactions in bone result

[It is difficult to understand how identical circulatory derangements or insufficiency can cause atrophic arthritis in one case, hypertrophic arthritis in another The two pathologic pictures are totally different As one of us has stated, one must distinguish sharply between the application of the theory of circulatory deficiency to atrophic and to hypertrophic arthritis¹⁹² When patellar vessels are ligated and the blood supply is sharply diminished, resulting alterations in bone are chiefly hypertrophic, not atrophic This is what one would expect if one accepts the recent dictum of Jones and Roberts (1934) that bone undergoes increased calcification if its blood supply is decreased, but it undergoes decalcification if its blood supply is increased If this is true, the theory of circulatory deficiency would seem much more applicable to hypertrophic than to atrophic arthritis, and in the latter disease one might better search for an augmented, not a decreased blood supply to account for atrophy of bone in atrophic arthritis Such a state has been suggested as being present in the form of hypéremia and formation of new vessels—Ed]

Factor of altered nutrition In "many cases" Gammon²⁹⁴ and Archer¹⁴⁶ found decreased sugar tolerance However, Archer felt that the evidence of obesity, hypertension and endocrine disturbances probably accounted for it Gammon also mentioned abnormal purine tolerance in many cases

[Statements similar to this last are frequently made, in general without adequate evidence in support thereof By the endless repetition of such unsupported opinions, these ideas become fixed in the literature Exhaustive research has failed to disclose a related purine abnormality—Ed]

Endocrine factors The presence of endocrine abnormalities was vaguely mentioned by many who continued to fail to produce definite evidence of them Thus, we read that metabolic disturbances "unquestionably play a prominent rôle, as manifested by the gratifying response to reduction in weight and compensation for endocrine deficiencies by the use of thyroid extract and ovarian and pituitary hormones"¹⁷³

[This is another example similar to the one just commented on. It is agreed that reduction of the trauma of obesity is of great importance in hypertrophic arthritis. Therein lies the value of thyroid extract. None but a weight-reducing effect has ever been proved for it, and in a disease presumably the result of catabolism in excess of anabolism, it is difficult to see how the administration of thyroid extract could help matters. The value of other than weight-reducing endocrine substances in this disease remains entirely unproved.—Ed.]

Factor of infection. The ideas of several writers, in this regard, have been noted previously. For example, Brooks¹¹² expressed the belief that the disease is of staphylococcal origin (no supporting data given). Trauma is usually considered the cause of the symptomatic exacerbations of quiescent or relatively symptomless hypertrophic arthritis. Key¹⁸⁴ expressed the opinion that sometimes this idea is scarcely tenable, and that infection of low grade may produce symptoms in cases of the disease which, like the majority of cases, would otherwise be symptomless.

Because cases of osteo-arthritis and spondylitis osteo-arthritica (atrophic spondylitis) presented but few high antihemolysin titers (in contrast to those of atrophic arthritis) Griffiths¹⁰⁶ looked on the disease as noninfective.

Conclusions on etiology. We can but conclude, as formerly, that the disease is of unknown origin but is obviously conditioned by age and is aggravated, pathologically and symptomatically, by trauma and, some would add, perhaps to a less extent by infection and other less well-defined abnormalities of nutritional, circulatory and endocrine nature.

Treatment. Removal of foci. It has been noted that Steindler²¹² found foci of infection in only 17 per cent of his cases and that removal of these foci gave real relief in only 8 per cent of those cases in which it was done. The majority of writers continue to agree that removal of foci does not particularly affect the course of the disease.^{148, 295}

Diet. Sladen, Ensign and McColl¹⁹⁰ rearranged the type, and Scull and Pemberton²⁹⁶ reduced the amount of carbohydrates, ascribing benefit to such dietary measures in cases of hypertrophic, as well as in cases of atrophic arthritis. Tissue edema, also occasionally present in cases of hypertrophic arthritis, may be thus reduced. The majority of writers contented themselves with correction of traumatizing obesity, if present.^{121, 175}

Vaccines. These are but rarely recommended²²⁴, they are generally disapproved.¹⁴⁸

Histamine. This is recommended by some for hypertrophic, as well as for atrophic arthritis.²³²

[No acceptable data indicating its worth are at hand.—Ed.]

Mecholin iontophoresis. In general, the results of this method in cases of hypertrophic arthritis were no better than those derived from simpler measures.^{189, 234}

Blood letting. Kovacs advocated this measure in cases of hypertrophic arthritis in which "a plethoric state and high blood pressure are generally present."¹⁴⁰

[As a matter of fact, plethora is generally absent according to Sparks and Haden (1932), who found the blood volume 7 per cent below normal in 15 cases—Ed]

Physical therapy The usual physical therapeutic measures were advocated²³⁵

Fever therapy This has proved of little value. The early experiences of Tenney, Beiris and King have been reviewed previously.⁴ Simpson²² has treated about 25 patients, with disappointing results. They did not tolerate treatment well, and any relief obtained was transient.

Orthopedic operations When marked stiffness occurs orthopedic operations occasionally are performed.²³⁷

Prognosis Aside from those of Nissen¹⁵¹ and Nissen and Spencer¹⁵² no new data on prognosis are at hand. Kuhns²⁰² voiced the general opinion that when adequate therapy and protection are supplied for the joints, progressive deterioration is not inevitable, even among aged persons.

BACKACHE AND SCIATICA

Space for this review does not permit a synopsis of the voluminous but confusing and often contradictory literature on backache and sciatica, which are symptoms of many paravertebral disturbances and diseases. The editors have failed to recognize much that is particularly new in the year's numerous articles on these subjects, but several informative and representative reports are available on the following subjects dealing with the differentiation of types and causes of backache and the sciatic syndrome: backstrain²⁹⁸, postural backache²⁹⁹, traumatic backache⁹, postoperative and parturient backache³⁰⁰, reflex backache³⁰¹, low backache from disease of facets³⁰² or from paravertebral muscular insufficiency³⁰³, sacroiliac strain and subluxation with the treatment thereof by Baer's hyperflexion manipulation³⁰⁴, congenital malformations and spondylolisthesis, the relationship of sciatica to narrowing of the lumbosacral disk³⁰⁵ or to disease (fibrositis) of the piriformis muscle,³⁰⁶ and the behavior of the intervertebral disks in tuberculous, typhoidal or specific infectious spondylitis and malignancy.³⁰⁷ A brief history of backache was given by Wentworth.³⁰⁸

These reports again emphasize the importance of thorough physical and roentgenologic examination and the importance of considering all possibilities before making a diagnosis of rheumatism or arthritis without definite evidence of articular disease. Because bony spurs, large or small, are present, one must not assume that the condition is explained, many large spurs are symptomless, small spurs may cause considerable pain, but one must be sure spurs have not long antedated symptoms. In diagnosing a patient's disease, evaluating symptoms and ruling on compensation cases one must use certain physical maneuvers and therapeutic tests. Buckley³⁰⁹ cautioned that in preparing to testify at a compensation case the physician should remember the dictum "exaggeration is very common—just as common as malingering is rare. Exaggeration is the natural defensive mechanism of

one who fears he presents inadequate external evidence of the pain he feels "

Sciatica This condition was grouped by Burt³¹⁰ thus 1 Root sciatica (36 per cent of his 140 cases) is most commonly attributable to intervertebral arthritis or strain of the lumbar vertebrae and pressure from new growths 2 Trunk sciatica (17 per cent of his cases) is attributable to inflammation of the sciatic sheath, primary or secondary to inflammation in the gluteus maximus or piriformis muscles 3 Referred sciatica is attributable to inflammation in some structure supplied by the sciatic plexus (45 per cent of his cases)

The general treatment was outlined by Burt and by Yeomans,³¹¹ physical treatment by Wolf³¹² and the use of injections of alcohol, quinine-urea or thiosinamine by Thomson³¹³

[The complications and untoward sequelae that may attend the injection treatment of sciatica are not sufficiently stressed in these articles—Ed]

The production of 15 to 30 minutes of complete anesthesia by evipan sodium (a barbiturate) for use during the manipulative treatment of sciatica was recommended by Douthwaite³¹⁴

SPONDYLITIS

There is even more confusion in the clinical, pathologic and roentgenographic differentiation of types of arthritis of the spine than in similar differentiation of types of arthritis of peripheral joints There is a tendency on the part of some investigators to recognize two main divisions equivalent to atrophic and hypertrophic arthritis elsewhere and then to subdivide each group further Until better evidence is available, the majority have preferred to ignore subdivisions entirely or to consider them but minor variations of the two main types, namely, atrophic spondylitis (spondylitis rhizomelique or ankylosing spondylitis) and hypertrophic spondylitis (spondylitis osteo-arthritis)

[This viewpoint is favored by us—Ed]

Two reports illustrate these differences of opinion Miller³¹⁵ recognized two main types, Doub³¹⁶ approved of further subdivisions Miller considered "atrophic arthritis of the spine" to be synonymous with "spondylitis rhizomelique," and expressed the belief that the Marie-Strumpell type (spondylitis ossificans ligamentosa of Knaggs) and the von Bechterew type (spondylitis muscularis of Knaggs) are variations of the same process, not worthy of particular differentiation Doub favored Knaggs' separation of atrophic spondylitis under two subheadings spondylitis ossificans ligamentosa (Marie-Strumpell type) and spondylitis muscularis (von Bechterew type) Another type, called "spondylitis senilis," supposedly a variety of spondylitis muscularis as it appears among elderly persons, was listed by some under atrophic spondylitis, by others under hypertrophic spondylitis

Atrophic Spondylitis (Spondylitis Ankylopoietica) This is presum-

ably the spinal equivalent of atrophic arthritis and the same in its cause and general treatment. Miller qualified the synonymy by saying, "Rheumatoid (atrophic) arthritis of the spine is usually followed by pathologic changes recognized as spondylitis ankylopoietica. It is perhaps unnecessary to state that a patient with spondylitis ankylopoietica does not necessarily have rheumatoid arthritis of the spine. However, (the latter) leads to (ankylopoietic) changes." Doubt, urging further subdivision, stated that spondylitis ossificans ligamentosa and spondylitis muscularis are similar only in that both are characterized by spinal ankylosis and dorsal kyphosis. "It seems rather odd that they should be considered stages of the same process. Their pathology, signs, symptoms and development are quite different, and the etiology as given by most authors is also distinct."

[No original data are given in proof of these statements—Ed.]

Presumably the differentiation is as given in table 1

TABLE I
Characteristics of Spondylitis

	Spondylitis ossificans ligamentosa		Spondylitis muscularis
Situation	Spinal column, sacro iliac joints, hips, shoulders		Not in hips or shoulders
Progression	Ascending type, from lumbar region		Descending type, from cervicothoracic region
Appearance	Thoracic region	Flat, immobile chest, kyphosis	Flat, immobile chest, kyphosis more marked
	Lumbar region	Generally straight	Generally lordotic
Pathology	Vertebral bodies	No marked change	Fusion at anterior margins
	Intervertebral disks	Little or no change	Atrophic, narrowed, may disappear
	Spinal ligaments	Calcification	No calcification
	Facets	Ankylosis through bony proliferation and ligamentous calcification	Not mentioned in current references
	Other areas	More a periarticular, calcifying fibrositis than an arthropathy	Muscular weakness, followed by secondary spinal changes, calcification is bony, not ligamentous

The incidence of atrophic spondylitis outside of special clinics for arthritis is, according to Miller,³¹⁵ not very great. Miller cited Schmorl and Junghanns (1932) to the effect that only eight cases were found among 10,000 postmortem examinations. Doubt was sympathetic to the idea of

Oppel (1929), of Ballin and Morse (1931) and of others who have included ankylosing spondylitis in the chapter on hyperparathyroidism

[No new evidence is presented We have stated previously⁴ that the evidence is entirely inadequate for us to adulterate the syndrome of hyperparathyroidism with any of these forms of arthritis—Ed]

Nothing new is offered in treatment

Hypertrophic Spondylitis (Spondylitis Osteo-Arthritica) This is similar to hypertrophic (degenerative) arthritis elsewhere in the body and is characterized, early, by flattening of the margins of the vertebral bodies, later by the formation of marginal exostoses or osteophytes, narrowing of the intervertebral spaces and eburnation Bony ankylosis is not the rule, spurs often impinge but do not unite The lumbar and midcervical portions of the spinal column generally are involved, the thoracic portion is much less commonly affected, at least symptomatically The condition has been found, roentgenographically, almost universally to affect patients who are more than 50 years of age (Garvin, 1927) Miller cited Schmorl's statistics on postmortem studies of 10,000 spines and in particular 4,253 macerated specimens Spinal osteophytes were not found in subjects who had been in the first two decades of life They were present in 11 per cent of those in the third, in 36 per cent of those in the fourth, in 78 per cent of those in the fifth, and in 93 per cent of those in the sixth decade

We have commented previously on roentgenographic and postmortem studies of the incidence of hypertrophic arthritis in other joints The studies of Keefer (1933) on knee joints have been extended by Keefer and Myers who cited age and trauma as causes of the condition and outlined a pathogenesis similar to that reported by Schmorl To Keefer and Myers,³¹⁷ the so-called exostosis represents, however, not overgrowth of bone but flattened portions of the margins of joints squeezed out by pressure

[This is not the opinion of most pathologists—Ed]

The accepted cause of hypertrophic spondylitis is degeneration from tissue-senility and trauma, particularly that incident to man's upright posture Ely³¹⁸ has reiterated his view that this form (spondylitis type II) is attributable to a living non-bacterial organism which causes aseptic necrosis, followed by secondary changes of traumatic arthritis Judging from his previous papers, he may mean an ameba He has expressed the belief that the causal organism enters the body from roots of dead teeth and is probably later domiciled in the intestines

[Ely admittedly never has been able to prove his suspicions No new evidence is given—Ed]

Miller traced Schmorl's ideas on pathogenesis as follows (1) loss of fluidity, fibrous desiccation and disintegration, first in the nucleus pulposus, then in the annulus fibrosus, (2) thinning and loss of resiliency of disks,

(3) increased mobility of involved vertebrae, (4) impingement of vertebral runs, producing trauma which leads to formation of osteophytes, and (5) increased strain on vertebral ligaments producing periosteal irritation and formation of new bone

Apropos of the factor of trauma, Buckley and Miller reminded readers of Beneke's (1897) observation that if a man is right-handed the largest lumbar osteophytes are on the left side and vice-versa

The symptoms originating from nerve roots, which may arise about the head, neck and arms, were listed again by Bisgard³¹⁰ (1934) Pseudo-angina pectoris may also originate from cervical involvement³²⁰

Nothing new on treatment has developed Bisgard expressed himself as favoring roentgen therapy Vernon³²¹ recommended paralgesia—para-vertebral block with procaine for relief of pain

THE FACET SYNDROME

In discussions on pathology of the spinal column, the vertebral bodies and intervertebral disks generally command attention—the facets are rarely noted The importance of diseased facets in the production of pain low in the back, with or without sciatica, has been emphasized only recently, in 1927 by Putti, and now by Ghormley³⁰² The articular facets are the only true joints in the spinal column, they may be affected by acute traumatic arthritis from fracture of them, by chronic traumatic arthritis consequent on narrowing of the fifth lumbar intervertebral space, or less commonly by infection The common pathologic findings place most cases of arthritis of the facets in the group of hypertrophic (degenerative) arthritis, resulting generally from trauma Pathologic change of the facets includes degeneration of its cartilages, hypertrophy and eburnation of underlying bone

The patient affected with the facet syndrome may complain of sudden onset of pain low in the back, brought on by some activity, often trifling in its severity but usually involving a twisting or rotary strain of the lumbosacral region Sciatic scoliosis and muscular spasm may ensue, until spasm subsides pain may persist The pains, static in type, can be relieved by assuming a certain posture, or can be exaggerated by assuming other postures, the pain is of a "locking type" Satisfactory demonstration of changes in facets, hitherto impossible, is now possible with the roentgenographic technic of Ghormley and Kirklin, an oblique or three-quarter view is taken³²² Ghormley advised conservative therapy in the form of recumbency with or without traction, physiotherapy, possibly epidural injections If these fail, manipulation or long recumbency in plaster of paris casts may be needed, or even lumbosacral fascetectomy, the technic of which Ghormley described By such a procedure, Mitchell³²³ recently provided relief in a case of sciatica in which there were a narrowed fifth lumbar interspace and subluxation of facets A curious case was reported by Greig³²⁴ A left perinephritic abscess developed Remnants of the abscess were discovered at necropsy

16 years later, with adjacent, localized, unilateral ossifying spondylitis. The chain of events was possibly as follows: recurrent inflammation, alternate hyperemia and congestion, repeated, localized, temporary decalcification with subsequent reformation of bone as the hyperemia subsided, and ultimate sclerosis of bone.

[Apparently roentgenograms were not made at any time—Ed.]

GOUT AND GOUTY ARTHRITIS

Symptoms and Course A very readable synopsis of current ideas on gout has been given by Lichtwitz^{3,5} who wrote that gout is always a chronic disease, a fact that should be recognized in the first attack of acute gouty arthritis, for attacks of arthritis are merely surface explosions of what, in the interim, is a more or less symptomless, but not necessarily a quiescent, disease. Lichtwitz recognized but did not clarify the entity, atonic gout. Modern gout affects the thin, nervous type of person more frequently than formerly.

Two cases were used by Hench³²⁶ to emphasize several points: 1. A history of acute, recurring attacks, with complete remissions, is of diagnostic importance; complete restitution of articular function after numerous early attacks is one of the most characteristic features of gouty arthritis, of itself almost diagnostic. 2. Joints other than those of the great toe may be affected, and those of the great toe may be long unaffected, in one case, in which 150 attacks took place, only 10 affected a big toe, whereas in the other case, in 20 out of 30 attacks a great toe was affected. 3. Roentgenograms may long be non-specific, even negative. 4. Repeal of prohibition already has been followed by an increase in incidence of gouty arthritis as seen at The Mayo Clinic (alcoholic imbibition being a precipitatory, not a causal, factor).

The provocative effect of a high-fat (220 to 300 gm.), low-carbohydrate (20 to 50 gm.) diet in cases of gout was noted by Lockie and Hubbard^{327, 328}. On such a diet, within two to six days, in each of four cases acute gouty arthritis developed. If the diet was maintained, hyperuricemia developed. Ketosis was not sought. A similar diet did not aggravate atrophic or hypertrophic arthritis.

Acute gout occasionally may be precipitated by administration of insulin (Rabinowitch, 1928). In this connection it is interesting to note the provocation of allergic arthritis (symptoms of serum-sickness, not of gout) in the case of a diabetic female after administration of insulin, a phenomenon which, according to the belief expressed by Johnson,³²⁹ may represent an unusual type of insulin allergy.

Associated and Complicating Conditions Acute and chronic gouty arthritis both have their symptomatic and physical differences—some obvious but others subtle—from atrophic arthritis, although the former may simulate the latter in some regards. The association of gouty arthritis with un-

mistakable atrophic arthritis is very rare according to those of wide experience with both diseases Cecil¹⁶⁵ reported the association in two cases

[Both of Cecil's patients undoubtedly had gout, but the diagnosis of atrophic arthritis is based on the presence of fusiform joints and positive agglutination of hemolytic streptococci. The former may occur in gout, the complete diagnostic significance of the latter is not accepted by all. From data given we cannot accept the association as proved in these cases—Ed.]

Gout of adults not infrequently is associated with blood dyscrasia, pernicious anemia when treatment with liver is being given, leukemia, and polycythemia. Some investigators say gout is merely a symptom of destruction of nuclei of blood cells. Vining and Thomson³³⁰ have reported the association of gout with aleukemic leukemia in the case of a boy aged five years.

[No blood chemical studies were reported—Ed.]

A case of erythremia, migraine, gout and intracardiac thrombosis was reported by Weber³³¹

Etiology and Pathogenesis Lichtwitz³²⁵ agreed with the idea that uric acid is nontoxic and not the cause of gout. The symptomatic activity of gout and the production of gouty arthritis do not parallel the degree of hyperuricemia. He favored the allergic theory of gout, allergens are both exogenous (food and drink) and endogenous (tissue substances formed after injuries, surgical operations, sharp vasomotor disturbances). In this connection the opinion of Eaton and Love³³² should be noted: chronic arthritis (especially the atrophic type), may be an allergic disease, with excess of uric acid in synovia and blood acting as the predisposing agent.

[Hyperuricemia is occasionally seen in cases of atrophic or hypertrophic arthritis, but it is the unusual, not the usual, finding. Since the mechanism and significance of hyperuricemia is but little understood and allergy and allergic arthritis even less clear, these remarks must be considered highly speculative—Ed.]

Treatment The patients of Lockie and Hubbard, when placed on a high-carbohydrate (350 to 400 gm.) diet, promptly recovered from their attacks which were induced by high-fat diets. It is advocated, therefore, that patients who have gout avoid fats and accept a generous intake of carbohydrate. The purine-free diet is more highly regarded by the physician than by his patient, according to Lichtwitz, who prescribed it only for four to six weeks after an attack, a low-purine, low-meat diet thereafter. When large tophi are present their removal is indicated to prevent juxta-articular ulceration, which may necessitate amputation of phalanges, and to relieve the kidneys if possible, according to Hench³²⁶. Theoretically, removal of large tophi (weighing 10 to 300 gm.) may relieve the kidneys of the work of many weeks or months. These are but mathematical speculations, Hench admitted, and how much relief is afforded the kidney in gout, by removal of large tophi is problematic, since the factors which govern

resorption and excretion of tophaceous material are but little understood. Cinchophen should be used only intermittently and with great caution, according to Copeman³³³ and Lichtwitz. However, the use of tolysin (neocinchophen) in moderate doses (5 grains three times a day for four weeks) produced in 120 patients who had "traumatic arthritis" or "infectious arthritis" no functional alterations in liver or kidneys detectable by Stein and Minnich.³³⁴

[The editors do not favor the use of cinchophen whenever an efficient substitute is available, such as acetylsalicylic acid, in treatment of atrophic or hypertrophic arthritis. It would appear⁴ that there is no physiologic equivalent for cinchophen in the presence of gout, and since most cases are not long controlled by diet alone, the careful intermittent use of cinchophen seems justified. The doses of cinchophen, in tolysin, were not great enough or given long enough to justify drawing conclusions on the toxicity of tolysin—Ed.]

Quick,³³⁵ who expressed belief that cinchophen poisoning is an allergic manifestation, and acute yellow atrophy a special form of Arthus' phenomenon, wrote that the schedule of intermittent dosage (Graham, 1927) is not protective, indeed may favor the development of hypersensitivity.

In the translation of a fourteenth century French manuscript on gout, Saye³³⁶ found a modern note—a statement promising relief from pain but not complete recovery.

Experimental Gout and the Problem of Uric Acid Spontaneous gout occurred in turkeys raised by Schlotthauer and Bollman.³³⁷ Tophi and hyperuricemia (to 16 mg per 100 c c of blood) were present. Secretion of uric acid varied with the amount of food taken, not with the amount of uric acid in the blood. The latter increased, decreased, or remained unaltered during periods of widely divergent excretion of uric acid. The fertility of eggs from gouty flocks was greatly diminished. Eggs had an increased content of urate, but not in proportion to the concentration in the blood. Factors of sex and age seemed unimportant. Experimental gout was later produced in 20 turkeys.³³⁸ Tophi appeared only in those in which hyperuricemia of 15 mg per cent developed and remained for at least two weeks.

The provocative effect of a high-fat diet in the cases of Lockie and Hubbard was in part explained by Quick.^{339, 340} Excretion of uric acid can be accelerated by various antiketogenic compounds (glucose, glycerol, pyruvic acid, glycine, alanine, aspartic acid, glutamic acid), also by a high-protein diet. It can be depressed by ketosis and by lactic acid, whether fed or produced in excess in the body, also by benzoic acid, phenylacetic acid, and similar compounds. Ketosis probably accounts for the hyperuricemia of fasting, or when a high-fat diet is employed, or in severe diabetes, excess accumulation of lactic acid may explain the high concentration of uric acid in the blood, which often is present in eclampsia, chloroform poisoning, pneumonia, circulatory failure, and other anoxemic states. Retention of uric acid after ingestion of sodium bicarbonate probably is attributable to the corrective formation of excess lactic acid.

[Since the patients of Lockie and Hubbard ingested 20 to 50 gm of carbohydrate daily, it is doubtful whether ketosis was present because it is very difficult, if not impossible, to produce ketosis with a high-fat diet unless the intake of carbohydrate is less than 15 to 20 gm—Ed]

Other interesting studies on the problem of uric acid which can only be mentioned are that by Martin and Corley³⁴¹ on the excretion of allantoin and uric acid by dogs on a purine-free and on a protein-free diet, as affected by glycine, the work of Gersh³⁴² suggesting that in rabbits, at least, uric acid is not eliminated by renal tubules but by glomeruli, the inability of Ranganathan³⁴³ to produce uric acid calculi in rats by causing them to ingest an excess of uric acid, the uric acid content of human and animal lymph, blood, aqueous humor, and cerebrospinal fluid, as analyzed by Walker³⁴⁴, and the studies of Pritham and Anderson³⁴⁵ on the comparative value of various methods for the determination of uric acid in blood

HEMOPHILIC ARTHRITIS

A brief but interesting historical sketch was presented by Birch,³⁴⁶ with a summary of accepted clinical and laboratory data on hemophilia, and a restatement of her ideas (1932) on the cause, namely, that it is an ovarian deficiency. This is but theory, and the cause remains unknown. Hemophilia, occasionally occurring when no ancestor has been known to be a bleeder, is called "sporadic" or "spontaneous" hemophilia. Even so it does not arise *de novo* but is undoubtedly inherited from a recessive mother, according to Boggs³⁴⁷ who reported six cases of hemarthrosis in brothers. The likelihood of concealed inheritance seemed precluded, as there was no trace of bleeders in five generations of the mother's ancestry. Therefore the writer, scientifically although not gallantly, raised the question of the mother's illegitimacy. It is generally believed that hemophilia does not exist among females (Bauer and Wehefritz, 1926). Foulis and Crawford³⁴⁸ expressed their inclination to believe that it may, and they presented in evidence the cases of two sisters, members of a known hemophilic family. One sister had a prolonged clotting time, and her two sons were hemophiliacs. The other sister had been in extremis once following extraction of a tooth and recently had had severe postpartum hemorrhage, not of the ordinary type but a vaginal hemorrhage. Purpura was considered unlikely particularly in view of the family history.

[The data were very meager—Ed]

From a total of eight cases, Kahn,³⁴⁹ Rypins³⁵⁰ Solis-Cohen and Levine³⁵¹ confirmed the presence of articular roentgenographic alterations previously noted.⁴ These include when seen early, distention of the capsule, widening of joint space, an articular shadow denser than that encountered in ordinary synovitis and irregular areas of density (blood pigments) suggesting calcification, seen later, there are spotty destruction of

cartilage, broadening of femoral condyles, widening of intercondylar space, formation of cavities or cysts from subperiosteal or subchondral hemorrhages and fibrous or bony ankylosis. Late roentgenograms may simulate those of tuberculous, atrophic, hypertrophic or other types of arthritis. There is no pathognomonic sign.

Treatment To Birch, the rationale of whole ovarian extract is obvious. 40 to 120 grams are given daily by mouth, or 50 to 200 rat units are given subcutaneously or intramuscularly, and have afforded best results. Cotton soaked with ovarian extract is applied to open bleeding areas such as dental sockets. One of Rypins' patients "did remarkably well" under treatment with ovarian extract. Others were disappointed with treatment by ovarian hormone (Stetson, Forkner, Chew, and Rich³⁵², Brem and Leopold³⁵³, Lureen³⁵⁴). Hemarthrosis was not benefited or prevented, and no related alterations in coagulation time of blood or of urinary estrogenic substances were observed in a total of eight cases in which treatment was with ovarian tissue given orally, or various ovarian extracts, estrogenic substances or theelin given parenterally. The relationship between hemophilia and female sex hormones was doubted.

[Further study is necessary to determine whether the use of ovarian extracts is more potent than the use of other non-specific tissue extracts—Ed.]

Pituitary extracts were not helpful in one of Birch's cases. MacFarlane and Barnett³⁵⁵ suggested the local application of sterile solutions of snake venom (*Vipera russelli*) in a dilution of 1 in 10,000 or even 1 in 100,000 parts. Blood of hemophiliacs which clotted spontaneously in 35 minutes, clotted in 17 seconds when one drop of 1 in 1,000 solution was added to 10 drops of blood. In the dilutions used, toxins apparently have been diluted beyond harm. Older methods of therapy were reviewed by Birch and by Kugelmass³⁵⁶: tannic acid dusting powder, application of raw meat or fresh blood, avoidance of disturbing dressings that adhere to wounds, cold applications the first 24 to 48 hours, later warm applications, goat serum given intradermally, transfusion or intramuscular injection of blood, for joints, elevation of the part, absolute rest, application of a posterior splint to prevent contractures, physiotherapy cautiously.

PSORIATIC ARTHRITIS

Many cases are being reported in European continental, few in English or American, literature. One case was reported by Sharma,³⁵⁷ who, vaguely believing that the condition might be of endocrine origin, gave ovarian substance. A month later the psoriasis had cleared up, the joints were "cured," and although psoriasis later recurred, the arthritis did not.

[The data are entirely inadequate to justify conclusions—Ed.]

ALLERGIC, METABOLIC AND ENDOCRINE ARTHRITIS

These terms are appearing less frequently to plague the reader. The year's reports included nothing to clarify their vagueness in any way. The possible predisposing or precipitating importance of such factors as allergic reactions to food (we have discussed bacterial allergy elsewhere), or metabolic or endocrine abnormalities, is worthy of consideration and has been touched on by many investigators, most directly by Johnson³²⁹ in his description of allergic arthritis from insulin, by Eaton and Love³³² in their discussion of the relationship of chronic arthritis and hyperuricemia to allergy, and by Cavadias,³⁵⁸ who concluded that, although chronic rheumatism is a disease which exhibits important metabolic disturbances, it is not characterized by one consistent, classifiable metabolic derangement as is diabetes.

DISEASES OF MUSCLES AND FIBROUS TISSUES (INCLUDING FIBROSITIS AND MUSCULAR RHEUMATISM)

Fibrositis To some this term is merely an impressive name for any vague ache or pain in the neighborhood of muscles or tendons. To others it is the name of a definite pathologic condition, which is an inflammatory exudation in and hyperplasia of white fibrous tissue anywhere in the body, acute or chronic in type, characterized by formation of nodular indurations appearing in various sizes, situations, and manifesting varying degrees of tenderness. Some accept an anatomic differentiation: intramuscular, fascial, bursal, perineural (of which sciatica is often a type), capsular, periarticular, or subcutaneous (panniculitis)^{379, 380}. Since an inflammatory reaction in fibrous tissue occurs in rheumatic fever and various types of arthritis, Jones³⁶¹ would include them also under the general term, and would speak of "fibrositis of rheumatic fever," of "gout," of "rheumatoid arthritis," or of "osteo-arthritis." In general, however, the term is limited to diseases of periarticular and nonarticular structures. Some writers use clinical or etiologic terms: "traumatic," "infectious," "toxic," "senile fibrositis."^{362, 363} The nomenclature of fibrositis thus reveals the same gropings for order amid confusion, the same general etiologic alignments, which exist in arthritis.

Etiology The exact cause is unknown. That trauma of overexertion (exercise or fatigue) can produce the condition seems clear, but traumatic fibrositis or myositis must not be diagnosed in a haphazard manner. A number of conditions may masquerade as traumatic fibrositis or "charley-horse." Elsom³⁶⁴ listed them: simple contusions, muscular strain or rupture, actual myositis with or without calcifying hematoma, periostitis and tenosynovitis. Other presumed causes are chilling or dampness, streptococcal infection, bacterial toxins, "bowel toxins", and acid by-products of fatigue, especially lactic acid. Some consider the condition to be neuralgia of sensory nerves, others believe it is merely a manifestation of neurasthenia.^{6, 359, 360, 362, 363, 365} Many writers are very definite in their opinions,

vague in their terms. Thus, Albee was certain that fibrositis is caused by toxins, particularly those derived from the colon, but he wrote of the condition occurring with the gouty diathesis, with excess of uric acid, with cirrhosis of liver, and so on, and he used estimations of the histamine content of the stools as an index of toxicity.

[Not the least evidence of any sort concerning etiology is offered by many of these writers—Ed.]

Symptoms These may be acute or chronic and may include muscular tenderness and stiffness, muscular spasm (if acute), tenderness over insertions of tendons, small, tender indurations, or actually palpable nodules. Symptoms are exhibited particularly when affected tissues are put on a stretch. The regions chiefly affected are muscular and fibrous tissue about the shoulders (capsulitis) and in the occipital or suboccipital regions, but particularly in the lumbosacral regions (gluteal and hamstring muscles). In the situation last named, which he felt was the major site, Albee wrote that the left side was affected 10 times more often than the right.³⁶³

Pathology The studies of Stockman³⁶⁵ constitute almost the only definite information we have on pathology, and even these were subject to the dubious inquiry of some.²⁷⁷ To some writers nodules are very elusive. Others find them without difficulty.³⁵⁹ At first there is merely a very low grade of inflammatory fibrous reaction, with exudation. Later the exudate may organize, and nodules and indurations may appear.³⁶⁵ In Pennington's cases sensitive nodules were found most frequently in the gluteal muscles, next most frequently in muscles about the shoulders, and less frequently in intercostal or paravertebral muscles. Almost 40 per cent of the gluteal nodules were symptomless. From the fact that such nodules are found so often in normal persons he deduced that fibrositis can be a transient, functional change from overuse of muscles. A second type of fibrositis is the "pathologic form" which may or may not be infectious. Fatigue, loss of muscular resiliency, chilliness, and vague muscular pains are almost universal in senility—signs of senile fibrositis so common that the term "senility" may be said to be synonymous with "fibrositis." In the other forms, the functional pathologic changes are transient, correctable and reversible. In the senile form, they are permanent, according to Pennington.³⁶²

Treatment Proposed methods of therapy concern (1) elimination of foci of infection or of toxins, (2) attention to painful muscles, (3) elimination of sensitive nodules. Albee wrote that he relied on colonic irrigations, acidophilous milk, a diet low in residue and in meat, substitution of lactose for table sugar to reduce production of bacteria and toxin in the bowels. Some rely strongly on physiotherapy, but Stockman expressed the view that although heat is of some service, spa-therapy is useless. Some urge light massage, others insist on firm massage over the nodules as the only way to relieve the condition. If the nodules cannot be dispersed one can "render them hard, callous and insensitive" by massage.^{364, 366} Young,²⁷⁷ however,

found it "difficult to understand how fibrous nodules can be excised by massage" To increase excretion of lactic acid, general sweating was urged by Pennington Some use intramuscular injection of quinine and urea hydrochloride into the tender spots³⁶⁷ Histamine can completely cure the condition, according to Mackenna²³³

[Our information on fibrositis or muscular rheumatism is much more incomplete and contradictory than is the case with other types of rheumatic disease It is indeed curious that excellent pathologic data are at hand on arthritis, in which affected tissues are much less available for biopsy than are those involved in fibrositis Until chemical, pathologic and bacteriologic studies on fibrositis are extended, little hope can be entertained for clarity Practically all articles on the subject give evidence of considerable copy-work, Stockman is one of the few, if not the only, writer who speaks with authority, he at least has made a good beginning The discussions of most of the writers are highly theoretical, and their treatment uncontrolled—Ed]

Epidemic Myositis or Pleurodynia (Devil's Grip, Bornholm Disease) Four reports tell of a recent epidemic of this disease along the Atlantic seaboard of this country and in Yorkshire, England^{368 to 371}

Other names for the condition are "myositis acuta epidemica" and "devil's clitch" Eighty cases are included in the four reports It is an acute infectious disease of unknown cause, characterized by an abrupt onset of excruciating pain in the chest, epigastrium, or along diaphragmatic attachments, fever, aggravation of the pain on deep respirations and movements of the trunk, disappearance of fever in four to 48 hours, in most cases recurrence of pain and fever after two or three days, invariable recovery without sequelae, occurrence among otherwise healthy persons of either sex, especially children, absence of significant pulmonary or pleural signs, a variable leukocyte count (17,000 to 3,000 per cubic millimeter of blood), and often leukopenia No reports on studies of the pathology are available The condition may be mistaken for early acute pneumonia or for an acute abdominal condition Laparotomy often is performed by mistake Absence of vomiting is of diagnostic help Treatment is that of acute pleurisy isolation of the patient, rest, analgesic drugs, reassurance

Myositis Ossificans Progressiva Only about 150 cases are recorded Two have been reported recently^{372, 373} The classical findings were present and do not need repetition here⁴ Interesting roentgenograms were included, and the difficulty of early diagnosis, when roentgenograms are negative, was stressed

BURSITIS

As we have noted, bursitis is pathologically a form of fibrositis However, it may be considered in a separate division here

Subdeltoid or Subacromial Bursitis An inflammation in the general region of one of these bursae generally takes the name of the adjacent bursa The calcareous deposits which often occur, however, are not in the bursae as a rule but in the supraspinatus tendon and, according to Gwynne and Robb,³⁷⁴ probably result from tears of the insertion of the supraspinatus

muscle Grossman³⁷⁵ has reviewed 375 cases and Rogers³⁷⁶ 100 cases Grossman expressed a preference for the term "periathritis," which Rogers rejected, since there is insufficient evidence that infection is present The usual symptoms are recounted and the usual ideas on cause are held—trauma and infection³⁷⁷ We are reminded that the calcareous deposits are often transient, and that the condition generally responds to conservative treatment Aspiration is advised by some

Prepatellar Bursitis and Ganglion In three painful cases of the former and 10 of the latter, the condition was inactivated by Eising³⁷⁸ and by Kaplan³⁷⁹ with a very few injections of sodium morrhuate This substance should not be used if the bursal sacs connect with joints or tendon sheaths

Iliopsoas Bursitis This is an unusual affection, sometimes difficult to diagnose In two cases in which trauma was a factor cure was brought about by Ramage and Morton³⁸⁰ by excision

Information on the development and structure of bursae is all too meager Two reports provided data thereon Since he found no subcutaneous olecranon or prepatellar bursae in fetuses, Black³⁸¹ expressed the belief that they develop after birth Neither subfascial nor subtendinous bursae are present in fetuses but subacromial bursae are Chandler³⁸² found iliopsoas bursae present before birth and rarely absent in adults In 15 per cent of cases, a communication between adjacent bursae and the hip joint exists, this communication is not the result of development but is produced by friction of the iliopsoas tendon

MISCELLANEOUS CONDITIONS

Lymphatic Leukemia Resembling Rheumatic Fever This condition occasionally is seen Articular symptoms resembling those of acute rheumatic fever may be prominent in cases of acute leukemia of children The literature was reviewed by Sutton and Bosworth,³⁸³ who presented the case of a child 32 months old At first fever and swollen joints were associated with enlarged nodes but not with an enlarged liver or spleen Blood counts were normal A diagnosis of rheumatic fever was entertained without satisfaction since salicylates were ineffective and carditis was absent Some months later the liver and spleen became enlarged, biopsy of a lymph node confirmed the diagnosis of leukemia Permission for necropsy was refused

Lipomas of the Articular Capsule These were successfully removed from three patients by Ghormley³⁸⁴

Calcification in Fat Pads about Joints This was noted by Ferguson³⁸⁵ in four cases

PHYSIOLOGY OF ARTICULAR STRUCTURES

Studies on the fundamentals of articular physiology are indeed meager The viscosity of synovial fluid is attributable to its content of mucin When this is removed the viscosity drops to that of a simple exudate Studying

lubrication of joints of horses Jones,³⁸⁶ an engineer, concluded that the coefficient of friction of a joint that has dried is nearly 14 times as high as when it is lubricated by synovial fluid or normal saline solution. A joint of which the surfaces are not lubricated is quickly destroyed when worked under a light load. It is imperative to study the problem of lubrication in joints of human beings in order to understand arthritic changes.

From his studies on the joints of rabbits and of human beings Kuhns³⁸⁷ concluded that lymphatic structures are as abundant as are small blood vessels in the tissues lining joints especially in synovial membrane. Lymphatic drainage of the joints of the lower extremities is through deep lymphatic structures to the popliteal deep femoral and iliac nodes. Synovitis prevents lymphatic absorption of material larger than molecular size, obliteration of lymphatic structures occurs with chronic inflammation. Kuhns and Weatherford³⁸⁸ have shown that colloidal and particulate matter may be carried to joints from body tissues and from the intestines through the action of cells of the reticulo-endothelial system. Such transported substances are stored in histiocytes in subsynovial villi. Large amounts are stored in bone marrow, lesser amounts in intermuscular septa and articular fat pads. Mild inflammation in articular tissues tends to increase the deposition of injected substances. Local blocking of the reticulo-endothelial system is transitory and ineffective in preventing deposition of colloidal and particulate matter injected elsewhere.

The effect of immobilization of normal joints is controversial. After experimental immobilization of the ankles of dogs for from one to three months, Ely and Mensor³⁸⁹ noted the following: frequent periarticular swelling, and thinning irregularity, fibrillation, at times fibrin plaques and vacuolization of cartilages (but no fibrous adhesions) between the joint surfaces, and some encroachment on, and substitution of, cartilage by connective tissue.

BIBLIOGRAPHY

The bibliography contains a few references to articles which should have been commented on in last year's review.

- 1 VAN BRUFEMAN, J. The complicated simplicity or the simple complicity of the rheumatism problem. *Acta rheumatol*, 1934, vi, 2-3.
- 2 LOMBARD, H. L. Chronic rheumatism, *Pub Health Nursing* 1934, xvi, 241-244.
- 3 EDSTROM, G. The incidence of rheumatic disease in certain occupations, *Acta rheumatol*, 1934, vi, 65-67.
- 4 HENCH, P. S., BAUER, W., FLETCHER, A. A., GHRIST, D., HALL, F., and WHITE, T. P. The present status of the problem of rheumatism: a review of recent American and English literature on "rheumatism" and arthritis, *ANN INT MED*, 1935, viii, 1315-1374, 1495-1555, 1673-1697.
- 5 CLIMIE, A. Chronic rheumatism, *Trans Roy Med-Chir Soc*, 1933-1934, xxviii, 21-26.
- 6 ADAMSON, R. O. Chronic rheumatism, *Trans Roy Med-Chir Soc*, 1933-1934, xxviii, 16-21.
- 7 O'CONNOR, D. S. A rational approach to an understanding of the arthritides, *Yale Jr Biol and Med*, 1934, vii, 41-46.

- 8 KEY, J A Contusion of cartilage as an etiological factor in chronic arthritis, Surg, Gynec and Obst, 1934, lviii, 166-170
- 9 JLPSON, P N Traumatic backache, Jr Am Med Assoc, 1933, ci, 1778-1782
- 10 GILBER, L J, and GOLDBERG, S A roentgenologic consideration of the arthritides, Radiology, 1934, xxiii, 45-50
- 11 KEEFER, C S, MYERS, W K, and HOLMES, W F, JR Characteristics of the synovial fluid in various types of arthritis, Arch Int Med, 1934, liv, 872-887
- 12 GLISSAN, D J Treatment of water on the knee, Med Jr Australia, 1934, ii, 430-431
- 13 KEEFER, C S, and MYERS, W K Gonococcal arthritis a clinical study of 69 cases, ANN INT MED, 1934, viii, 581-594
- 14 MEAD, C H, and STEWART, R I Peripheral arterial thrombosis, secondary to gonorrheal arthritis and intramuscular injection of milk, Arch Surg, 1934, xlix, 49-53
- 15 KEEFER, C S, PARKER, F, JR, and MYERS, W K The histologic changes in the knee joint in various infections, Arch Path, 1934, xviii, 199-215
- 16 First Report of the Neisserian Medical Society of Massachusetts The management of gonorrhea I The laboratory in the diagnosis of gonorrhea, New England Jr Med, 1934, ccx, 362-365
- 17 MCLEOD, J W, COATES, J C, HAPFOLD, F C, PRIESTLEY, D P, and WHEATLEY, B Cultivation of the gonococcus as a method in the diagnosis of gonorrhea with special reference to the oxydase reaction and to the value of air reinforced in its carbon dioxide content, Jr Path and Bact, 1934, xxxiv, 221-231
- 18 LEAHY, A D, and CARPENTER, C M The isolation of *Neisseria gonorrhoeae*, Jr Bact, 1935, xlix, 36
- 19 THOMPSON, L A simple method of supplying carbon dioxide in jars for bacteriologic cultures, Am Jr Clin Path, 1935, v, 313-315
- 20 MYERS, W K, KEEFER, C S, and HOLMES, W F, JR The characteristics of synovial fluid in gonococcal arthritis, Jr Clin Invest, 1934, xiii, 767-776
- 21 MYERS, W K, and KEEFER, C S The gonococcal complement fixation test in the blood and synovial fluid of patients with arthritis, New England Jr Med, 1934, ccxi, 101-103
- 22 SIMPSON, W M Artificial fever therapy a report of researches at Miami Valley Hospital, Proc Staff Meet, Mayo Clin, 1934, ix, 567-571
- 23 JONES, A C Experiences with hyperpyrexia by diathermy, Arch Phys Therap, 1934, xv, 155-163
- 24 HEDRICK, D W Management of gonorrheal arthritis, Am Jr Surg, 1933, xxi, 255-261
- 25 KOVACS, R, and KOVACS, J Physical and constitutional measures in chronic arthritis, New York State Jr Med, 1933, xxxiii, 1148-1154
- 26 KOVACS, R Therapeutic hyperpyrexia with special reference to high frequency methods, Med Rec, 1934, cxl, 245-248
- 27 STAFFORD, O, and MARKSON, D E Electropyrexia a resume of therapeutic applications and technic, ANN INT MED, 1934, vii, 1391-1397
- 28 CARTER, H A Hyperpyrexia produced by physical agents (Report adopted by the Council on Physical Therapy of the Am Med Assoc), Jr Am Med Assoc, 1934, ciii, 1308-1309
- 29 OXFORD, T M Acute arthritis with analysis of cases, Tri-State Med Jr, 1934, vi, 1271-1274
- 30 HIGGINS, W H The commoner forms of arthritis, South Med Jr, 1934, xxvii, 793-796
- 31 TAYLOR, R L Gonorrheal arthritis treatment with Pregl's solution, Northwest Med, 1934, xlxiii, 371-372
- 32 HENDERSON, M S Tuberculosis of the joints, Journal-Lancet, 1933, liii, 403-406
- 33 HENDERSON, M S Surgical conditions of the knee joint, Am Jr Surg, 1934, xxvi, 499-512

- 34 GHORMLEY, R K KIRKLIN, B R, and BRAV, E A Tuberculosis of the knee joint a comparison of its morbid anatomy with its roentgenologic manifestations, *Am Jr Roentgenol and Radium Therap*, 1933, *xxv*, 747-755
- 35 BENNET, K, and HINRICSON, H A case of tuberculous infection of the knee joint, with clinical and roentgenographic appearance of Charcot's disease, *Jr Bone and Joint Surg*, 1934, *xxvii*, 463-466
- 36 FREUND, E Active and passive pleat formation of joint cartilage, *Arch Path*, 1934, *xviii*, 186-198
- 37 BRAV, E A, and HENCH, P S Tuberculous rheumatism a resume, *Jr Bone and Joint Surg*, 1934, *xxvii*, 839-866
- 38 LESAGE, A Tuberculous rheumatism, *Canad Med Assoc Jr*, 1934, *xx*, 30-37
- 39 BUCKLEY, C W Some points in the treatment of rheumatic diseases, *Lancet*, 1934, *ii*, 246-248
- 40 FAGGE, C H V Pneumococcal arthritis, *Guy's Hosp Rep*, 1933, *lxxviii*, 444-451
- 41 FARAH, N Subacute rheumatism due to a pneumococcus, *Lancet*, 1934, *ii*, 1102-1104
- 42 PAUL, J R, SALINGER, R, and ZUGER, B The relation of rheumatic fever to post-scarlatinal arthritis and postscarlatinal heart disease a familial study, *Jr Clin Invest*, 1934, *xiii*, 503-516
- 43 STEWART, W J Pseudo-arthritis of the hip following acute infection of the joint, *Ann Surg*, 1934, *xcix*, 515-516
- 44 KLAUDER, J V, and ROBERTSON, H F Symmetrical serous synovitis (Clutton's joints) congenital syphilis and interstitial keratitis, *Jr Am Med Assoc*, 1934, *ciii*, 236-240
- 45 GILL, A B, and ORR, T E Chronic synovitis of the knee with persistent or recurring effusion and of undetermined etiology, *Jr Bone and Joint Surg*, 1934, *xxvii*, 159-161
- 46 MILLER, J L Undulant fever, *ANN INT MED*, 1934, *viii*, 570-580
- 47 TWEDELL J T, and SCHLOTZHAUER, K B A case of undulant fever simulating acute rheumatic fever, with isolation of *Brucella abortus* in hemoculture, *Canad Med Assoc Jr*, 1934, *xxv*, 653-654
- 48 FELDMAN, W H, and OLSON, C, JR The reaction of swine following experimental inoculation of a pathogenic strain of *Brucella abortus* of porcine origin, *Am Vet Med Assoc*, 1934, *lxxv*, 64-75
- 49 PLACE, E H, and SUTTON, L E, JR Erythema arthriticum epidemicum (Haverhill fever), *Arch Int Med*, 1934, *liv*, 659-684
- 50 LOCKE, E A, and HAZARD, J B Haverhill fever (Erythema arthriticum epidemicum), *Trans Assoc Am Phys*, 1933, *xlvi*, 33-43
- 51 SCHARLES, F H, and SEASTONE, C V Haverhill fever following rat bite, *New England Jr Med*, 1934, *ccxi*, 711-714
- 52 MEEHAN, A V Treatment of suppuration in bones and joints, *Med Jr Australia*, 1934, *i*, 748-752
- 53 TAYLOR, G H Suppurative hip in children, *Jr Med Soc New Jersey*, 1934, *xxxi*, 458-460
- 54 JAFFE, H L Meningococcus arthritis and meningitis (case), *Jr Mt Sinai Hosp*, 1934, *i*, 23-25
- 55 GLOVER, J A, MILLER, R, WARNER, E C, LLEWELLYN, R L J, and others Discussion on aetiology of acute rheumatism and chorea in relation to social and environmental factors, *Proc Roy Soc Med*, 1934, *xxvii*, 953-972
- 56 CECIL, R L Present trends in the study of rheumatic fever and rheumatoid arthritis (The Jerome Cochrane lecture), *Jr Med Assoc Alabama*, 1934, *iii*, 361-370
- 57 NICHOL, E S Rheumatic heart disease in southern Florida (incidence and clinical notes), *Am Heart Jr*, 1933, *ix*, 63-71
- 58 SIMMONS, S T Rheumatic heart disease clinical data as observed in Louisville, Kentucky, *Am Jr Med Sci*, 1934, *clxxxvii*, 773-778

- 59 CHASL, A B Rheumatic heart disease, Jr Oklahoma State Med Assoc, 1934, xxvii, 1-3
- 60 MURPHY, J H Rheumatic fever in children, Nebraska Med Jr, 1934, xix, 424-427
- 61 OLESEN, R Heart disease a brief review of the etiology and incidence, and possibilities of preventing the disease, especially the rheumatic type, Pub Health Rep, 1934, xlix, 497-508
- 62 CLELAND, J B Rheumatic heart lesions in 3,000 Australian postmortem examinations, Med Jr Australia, 1934, ii, 382-385
- 63 JONES, E B The rheumatic child, Med Jr Australia, 1934, ii, 273-277
- 64 PAUL, J R, HARRISON, E R, and DEFORD, G K The social incidence of rheumatic heart disease a statistical study in New Haven School children, Am Jr Med Sci, 1934, clxxxviii, 301-309
- 65 KAISER, A D Factors that influence rheumatic disease in children based on a study of 1200 rheumatic children, Jr Am Med Assoc, 1934, ciii, 886-892
- 66 SWIFT, H F Chronicity of rheumatic fever, New England Jr Med, 1934, ccvi, 197-203
- 67 BENJAMIN, E L Some practical phases in juvenile rheumatism, Arch Pediat, 1934, li, 162-170
- 68 YOUNG, M A study of asthmatic and rheumatic children, with special reference to physical type, Jr Hyg, 1933, xxxiii, 435-463
- 69 FISCHER, V E Rheumatic heart disease at one year, Am Jr Dis Child, 1934, xlviii, 590-595
- 70 BLACK, R A Symptoms and treatment of the rheumatic child, Illinois Med Jr, 1934, lxxvi, 133-139
- 71 SCHLESINGER, B Clinical aspects of acute rheumatism in childhood, Acta rheumatol, 1934, vi, 29-32
- 72 HAWKING, F Latent acute rheumatic carditis as determined at autopsy its occurrence, Arch Int Med, 1934, liv, 799-804
- 73 GROSS, L, and EHRLICH, J C Studies on the myocardial Aschoff body I Descriptive classification of lesions, Am Jr Path, 1934, x, 467-488
- 74 ROTHSCHILD, M A, KUGEL, M A, and GROSS, L Incidence and significance of active infection in cases of rheumatic cardiovascular disease during the various age periods a clinical and pathological study, Am Heart Jr, 1934, ix, 586-595
- 75 KARSNER, H T, and BAYLESS, F Coronary arteries in rheumatic fever, Am Heart Jr, 1934, ix, 557-585
- 76 FRASER, A D Coronary endarteritis in acute rheumatism, Arch Dis Child, 1934, ix, 269-276
- 77 FRIEDBERG, C K, and GROSS, L Periarthritis nodosa (necrotizing arteritis) associated with rheumatic heart disease with a note on abdominal rheumatism, Arch Int Med, 1934, liv, 170-198
- 78 FELDMAN, S A, and GROSS, H Portal obstruction in rheumatic heart disease with adherent pericardium rupture of retroperitoneal varix with fatal hemoperitoneum, Am Heart Jr, 1934, x, 255-259
- 79 EASBY, M H A case of rheumatic heart disease with subarachnoid hemorrhage, Med Clin N Am, 1934, xviii, 307-310
- 80 BLAISDELL, J L The renal lesions of rheumatic fever, Am Jr Path, 1934, x, 287-297
- 81 KLEIN, J E Rheumatic pneumonitis report of a case, Arch Pediat, 1934, li, 736-739
- 82 ROSENBERG, W A Cutaneous rheumatic nodules, Arch Dermat and Syph, 1934, xxx, 377-384
- 83 CHESTER, W, and SCHWARTZ, S P Cutaneous lesions in rheumatic fever (predominating signs of active rheumatic fever during a ward epidemic), Am Jr Dis Child, 1934, xlviii, 69-80
- 84 HOLTZ, E, and FRIEDMAN, G A hemorrhagic eruption of the mouth and throat in the rheumatic state, Am Jr Med Sci, 1934, clxxxvii, 359-362

- 85 GUPTIL, P Differential diagnosis of abdominal manifestations of acute rheumatic fever from acute appendicitis, *Ann Surg*, 1934, xciv, 650-660
- 86 RILLA, L J Rheumatic peritonitis, *Am Jr Path*, 1933, ix, 719-724
- 87 STRUTHERS, R R, and BACAL, H L The relation of the sedimentation rate in rheumatic infection in childhood to alteration in the albumin-globulin ratio, *Canad Med Assoc Jr*, 1934, xxxi, 603-604
- 88 ELGHAMMER, H W Erythrocyte sedimentation rate in rheumatic infection, *Arch Pediat*, 1934, li, 281-287
- 89 PERRY, C B Sedimentation rate in rheumatic carditis, *Arch Dis Child*, 1934, ix, 285-294
- 90 OGILVIE, J W The gastric secretion in normal and rheumatic children, *Arch Dis Child*, 1934, ix, 327-333
- 91 PAYNE, W W Acid metabolism in rheumatic children, *Arch Dis Child*, 1934, ix, 259-266
- 92 KAISER, A D, and GRAY, M S Blood lipids in children with scarlet fever and rheumatic disease, *Am Jr Dis Child*, 1934, xlvii, 9-24
- 93 EASBY, M H, and ROESLER, H Changes in the S-T segment of the electrocardiogram in acute rheumatic fever, *ANN INT MED*, 1934, viii, 46-59
- 94 KOHN, L Changes in the T-wave of electrocardiogram in acute rheumatic fever, *Proc Soc Exper Biol and Med*, 1933, xxxi, 184-187
- 95 WOLFFE, J B Rheumatic heart disease—active and arrested, *Arch Pediat*, 1933, l, 832-850
- 96 PASCHER, F The tuberculin reaction in rheumatic fever, *Am Jr Med Sci*, 1934, cxxxviii, 537-541
- 97 BRADLEY, W H Pathogenesis of acute rheumatism, *Acta rheumatol*, 1934, vi, 23-25
- 98 BERTRAND, L The present position of research on the etiology of rheumatism experimental production of acute articular rheumatism in monkeys and chronic rheumatism and cataract in guinea pigs and rabbits, *Med Jr and Rec*, 1933, cxxxviii, 219-221
- 99 FARAH, N Acute articular rheumatism (maladie de Bouillaud) Is it really a polymicrobial syndrome? The role of pneumococcus as a specific agent Scarlatinal rheumatism Treatment of the focal infection by x-ray, *Jr Trop Med*, 1934, xxxvii, 321-325, 343-349
- 100 THOMSON, W A R Observations on the association of haemolytic streptococcal infection with acute rheumatism, *Brit Med Jr*, 1934, i, 1162-1164
- 101 HOWELL, K M, and BURTON, E P Dissociation of streptococci obtained from acute rheumatic fever, *Jr Infect Dis*, 1934, lv, 79-87
- 102 SMALL, J C The treatment of rheumatic carditis with aqueous extracts of streptococci, *Jr Lab and Clin Med*, 1934, xix, 695-705
- 103 JENKINS, C E The anaphylactic basis of rheumatism, *Brit Med Jr*, 1934, i, 186-189
- 104 PILOT, I, and DAVIS, D J Rheumatic diseases and sore throat with reference to hemolytic streptococci, *Illinois Med Jr*, 1934, lvi, 529-533
- 105 WEINSTEIN, I, and STYRON, N C Bacteriologic study of throats in rheumatic and non-rheumatic fever with special reference to hemolytic streptococci, *Arch Int Med*, 1934, lvi, 453-477
- 106 GRIFFITHS, G J Antihemolysin titres in chronic rheumatic and allied diseases, *Lancet*, 1934, ii, 251-252
- 107 MYERS, W K, and KEEFER, C S Antistreptolysin content of the blood serum in rheumatic fever and in rheumatoid arthritis, *Jr Clin Invest*, 1934, xiii, 155-167
- 108 WILSON, M G, WHEELER, G W, and LEASK, M M Antistreptolysin content of blood serum of children its significance in rheumatic fever, *Proc Soc Exper Biol and Med*, 1934, xxxi, 1001-1004

- 109 HADFIELD, G, MAGLE, V, and PERRY, C B Lysis of fibrin by streptococci its application to the problems of rheumatic infection in children, *Lancet*, 1934, i, 834-839
- 110 RINEHART, J F, CONNOR, C L, and METTIER, S R Further observations on pathologic similarities between experimental scurvy combined with infection and rheumatic fever, *Jr Exper Med*, 1934, lxx, 97-114
- 111 STIMSON, A M, HEDLEY, O F, and ROSE, E Notes on experimental rheumatic fever, *U S Pub Health Rep*, 1934, xlv, 361-363
- 112 EASON, J, and THOMSON, W A R The treatment of acute rheumatism by streptococcus antitoxin, *Edinburgh Med Jr*, 1934, xli, 583-591
- 113 FANTUS, B Therapy of rheumatic fever, *Jr Am Med Assoc*, 1934, cli, 2100-2101
- 114 LAWLER, E M Arthritis and rheumatic states modern therapy, *Jr Lancet*, 1934, liv, 9-13
- 115 SLOT, G, and DEVILLE, P M Treatment of arthritis and rheumatism with gold, *Lancet*, 1934, i, 73-76
- 116 SHANSON, B, and EASTWOOD, C G The use and action of histamine in rheumatism, *Lancet*, 1934, i, 1226-1228
- 117 MILLER, R VI Prognosis in juvenile rheumatism, *Lancet*, 1934, i, 1301-1302
- 118 COATES, G M, and GORDON, W Part played by tonsils and adenoids in the etiology of rheumatic fever, *Laryngoscope*, 1934, xlv, 876-884
- 119 STAHR, R Rheumatic heart infection in childhood, *Jr Iowa State Med Soc*, 1934, xxiv, 12-14
- 120 POYNTON, F J XIV The prevention of rheumatism, *Lancet*, 1934, i, 311-315
- 121 DOUTHWAITE, A H Diet in rheumatic disease, *Practitioner*, 1934, cxxxii, 65-71
- 122 ROCHE, C F, and JONES, T D Heart disease of the rheumatic type, *Jr Florida Med Assoc*, 1934, xx, 342-346
- 123 GILCHRIST, A R, and MURRAY-LYON, R M Does pregnancy hasten fatal termination in rheumatic heart disease? *Edinburgh Med Jr*, 1933, xli, 587-597
- 124 SCOTT, W A, and HENDERSON, D N Pregnancy and rheumatic heart disease, *Am Jr Obst and Gynec*, 1934, xxvii, 342-349
- 125 MUTCH, N The medicinal treatment of chorea (calcium aspirin), *Brit Med Jr*, 1934, ii, 246-249
- 126 COPEMAN, W S C Choreia its course and its treatment, *Indian Jr Pediat*, 1934, i, 94-98
- 127 SUTTON, L P, and DODGE, K G The treatment of chorea by induced fever, *Jr Pediat*, 1933, iii, 813-826
- 128 DON, C S D An unusual reaction to nirvanol, *Lancet*, 1934, i, 1230
- 129 SILBER, I B, and EPSTEIN, J W The treatment of chorea with phenyl-ethyl-hydantoin, a study of 28 cases, *Arch Pediat*, 1934, li, 373-382
- 130 MARICK, S W The nirvanol treatment of chorea, *Jr Pediat*, 1934, iv, 242-247
- 131 CALL, H F The nirvanol treatment of chorea, *Jr Indiana State Med Assoc*, 1934, xxvii, 216-219
- 132 CAPPER, A, and BAUER, E L Typhoid vaccine in the treatment of chorea, *Am Jr Med Sci*, 1933, clxxvi, 390-400
- 133 FISH, H Treatment of chorea by induced pyrexia, *Brit Med Jr*, 1933, ii, 816-817
- 134 REDFEARN, J A A new treatment for chorea, case report, *Jr Med Assoc Georgia*, 1934, xliii, 135-136
- 135 HOVERSON, E T The treatment for chorea by means of typhoid vaccine injections, *Illinois Med Jr*, 1934, lxxv, 556-559
- 136 MONTFORT J A Choreia treated with phenyl-ethyl-hydantoin and typhoid vaccine a comparative study, *Am Jr Dis Child*, 1934, xlvii, 1269-1278
- 137 Primer on Rheumatism chronic arthritis, *Am Med Assoc*, 1934, 52 pp
- 138 Report of the British Medical Association Committee on causation and treatment of arthritis and allied conditions, *Brit Med Jr*, 1933, i, 1033-1052

- 139 Reports on chronic rheumatic diseases, being the annual report of the British Committee on chronic rheumatic diseases appointed by the Royal College of Physicians, No 1, 1935, H K Lewis and Company, London
- 140 KOVACS, R, and KOVACS, J Chronic arthritis recent problems of its structural changes with special reference to physical therapy, Arch Phys Therap, 1934, v, 227-233
- 141 SHERWOOD, K K A new vaccine treatment of arthritis, Northwest Med, 1934, xxxiii, 78-81
- 142 BROOKS, C "Arthritis," New Orleans Med and Surg Jr, 1934, lxxvi, 551-557
- 143 HADEN, R L Problems of chronic arthritis, Jr Kansas Med Soc, 1934, xxxv, 1-6
- 144 HADEN, R L The classification of chronic arthritis, Physiotherapy Rev, 1934, xiv, 142-143
- 145 HADEN, R L The study and treatment of chronic (rheumatoid) arthritis one illustrative case, Med Clin N Am, 1934, xvii, 901-916
- 146 ARCHER, B H Chronic nonspecific arthritis etiology and treatment, with special reference to vaccine therapy, Jr Am Med Assoc, 1934, cli, 1449-1454
- 147 WETHERBY, M Chronic arthritis a clinical analysis of 350 cases, Med Bull Vet Admin, 1934, x, 282-297
- 148 SHAPIRO M J Modern conception of chronic arthritis, Minnesota Med, 1933, xvi, 719-728
- 149 BURBANK, R Arthritis considered as a systemic disease (role of streptococci), Jr Med Soc New Jersey, 1934, lxxxi, 522-525
- 150 WRIGHT, C S Chronic arthritis a curable and preventable disease further personal experience in the investigation and treatment, Canad Jr Med and Surg, 1933, lxxiv, 80-93
- 151 NISSEN H A Chronic arthritis and its treatment, New England Jr Med, 1934, ccx, 1109-1115
- 152 NISSEN, H A, and SPENCER, K A Arthritis and systemic involvement as exemplified in a group of dead arthritics, New England Jr Med, 1934, ccx, 147-149
- 153 OBER F R General aspects of chronic arthritis, New England Jr Med, 1934, ccx, 374-377
- 154 BURNETT, F L, and OBER, F R Arthritis, anabolic nutrition and health a study of the nourishment and health of joints, Am Jr Med Sci, 1934, clxxviii, 93-108
- 155 WOLF, H F New conceptions of arthritis and their relation to physical therapy, Arch Phys Therap, 1934, v, 405-408
- 156 THOMPSON H K A simplified concept of arthritis, New England Jr Med, 1934, ccxi, 370-371
- 157 GOLDTHWAIT, J E The differential diagnosis and treatment of the so-called rheumatoid diseases, Boston Med and Surg Jr, 1904, cli, 529-534
- 158 TAYLOR, G D, FERGUSON, A B, and KASABACH, H A study of the roentgenologic findings in various types of chronic arthritis, Proc Am Assoc, Study and Control Rheumatic Dis, 1934, 19-24 Also Proc Third Rheumatism Conference, Jr Am Med Assoc, 1934, clii, 1884
- 159 HOLBROOK, W P Evaluation of therapy in chronic atrophic arthritis, ANN INT MED, 1933, vii, 457-467
- 160 COX, K E, and HILL, D F Chronic arthritis serologic and clinical studies, Arch Int Med, 1934, liv, 27-39
- 161 BUCKLEY, C W The causes and treatment of arthritis, Brit Med Jr, 1934, i, 469-473
- 162 SENTURIA, B D The rôle of infection in chronic nonspecific arthritis, Jr Missouri State Med Assoc, 1934, xxxi, 229-231
- 163 MOLTKE, O Still's disease in adults a contribution to the symptomatology of sub-chronic polyarthritis, Acta med Scandinav, 1933, lxx, 427-453
- 164 VAN DER HOEVE, J Scleromalacia perforans, Arch Ophth, 1934, xi, 111-118
- 165 CECIL, R L Influential factors in recovery from rheumatoid arthritis, ANN INT MED, 1934, viii, 315-326

- 166 PEMBERTON, R, and BACH, T F A brief review of the treatment of chronic arthritis, *Med Clin N Am*, 1934, xviii, 107-131
- 167 STFINBERG, C L The Schilling differential in infections and in hypertrophic (degenerative) arthritis, *Jr Missouri State Med Assoc*, 1933, xxx, 485-487
- 168 RAWLS, W B, GRUSKIN, B J, RESSA, A A and JORDON, M The sedimentation rate and polymorphonuclear count in rheumatoid and mixed arthritis, *Jr Lab and Clin Med*, 1934, xix, 830-835
- 169 STAINSBY, W J, and NICHOLS, E E The clinical significance of erythrocyte sedimentation test in rheumatoid arthritis, *Jr Clin Invest*, 1933, xii, 1041-1049
- 170 McSWEENEY, C J Simple method of estimating sedimentation rate of red blood cells, *Lancet*, 1934, ii, 756-757
- 171 BRUGER, M, and POINDEXTER, C A The relation of the plasma cholesterol to obesity and to some of the complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis), *Arch Int Med*, 1934, lxi, 423-434
- 172 HARTUNG, E F, GREENE, C H, and BRUGER, M Calcium and cholesterol metabolism in arthritis, *Proc Am Assoc Study and Control Rheumatic Dis*, 1934, 14-18 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, cii, 1883-1884
- 173 DUNCAN, W Principles of treatment of chronic nonspecific arthritis, *Physiotherapy Rev*, 1934, xiv, 21-22
- 174 WALKER, F N Arthritis deformans, *Canad Med Assoc Jr*, 1933, xxix, 396-399
- 175 CECIL, R L The medical treatment of chronic arthritis, *Jr Am Med Assoc*, 1934, ciii, 1583-1589
- 176 SPRUNT, T P The treatment of the common types of chronic arthritis, *Virginia Med Monthly*, 1934, lxi, 448-455
- 177 DAWSON, M H, OLMSTEAD, M, and JOST, E L Agglutination reactions in rheumatoid arthritis III Comparison of agglutinins and precipitins for *Streptococcus hemolyticus* in rheumatoid arthritis sera, *Jr Immunol*, 1934, xxvii, 355-365
- 178 HITCHCOCK, C H Tissue reactivity to streptococci and its bearing upon the problem of arthritis, *New York State Jr Med*, 1934, xxxiv, 1022-1027
- 179 WAINWRIGHT, C W The treatment of chronic rheumatoid arthritis with streptococcus vaccine (on the basis of skin sensitivity), *Jr Am Med Assoc*, 1934, ciii, 1357-1361 Also *Proc Am Assoc Study and Control Rheumatic Dis*, 1934, 66-77 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, ciii, 1733
- 180 DAWSON, M H Discussion of paper by Wainwright¹⁷⁹
- 181 JONES, T D, and MOTE, J R Phases of foreign protein sensitization in human beings, *New England Jr Med*, 1934, ccx, 120-123
- 182 BLAIR, J E, and HALLMAN, F A Rheumatoid (atrophic) arthritis bacteriologic cultures of synovial fluid and of tissues, *Arch Int Med*, 1934, lxi, 87-96
- 183 BOYS, F, GUNN, F D, and LANG, S J Bactericidal power of blood in chronic arthritis, *Proc Soc Exper Biol and Med*, 1934, xxxii, 13-16
- 184 KRY, J A Personal futile attempts to prove the infectious origin of chronic arthritis, *South Med Jr*, 1933, xxvi, 1059-1062
- 185 SHORT, C L, DIENES, L, and BAUER, W Autogenous vaccines in rheumatoid arthritis a clinical study and critique, *Am Jr Med Sci*, 1934, clxxxvii, 615-623
- 186 WOLF, H Is arthritis an allergic disease? *Med Rec*, 1934, clxxxix, 527-530
- 187 BRAY, G W Recent advances in allergy, 1934, P Blakiston's Son and Company, Inc, Philadelphia
- 188 FREEMAN, J The present position of allergy and hypersensitiveness in chronic rheumatism and arthritis In *Reports on chronic rheumatic diseases*, 1935, H K Lewis and Company, Ltd, London¹³⁹
- 189 KOVACS, J The iontophoresis of acetyl-beta-methylcholin chloride in the treatment of chronic arthritis and peripheral vascular disease preliminary report, *Am Jr Med Sci*, 1934, clxxxviii, 32-36

- 190 KOVACS, J The peripheral blood circulation in chronic arthritis and the influence of vasodilators, *Proc Am Assoc Study and Control of Rheumatic Dis*, 1934, 25-33
Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, ciii, 1803-1804
- 191 WRIGHT, I S Discussion of paper by Kovacs ¹⁹⁰
- 192 HENCH, P S Discussion of paper by Kovacs ¹⁹⁰
- 193 NISSEN, H A, and SPENCER, K A Arteriosclerosis in the arthritic, *New England Jr Med*, 1934, ccv, 92-97
- 194 PEMBERTON, R, PEIRCE, E G, and BACH, T F The relation of vitamins to the dietetic treatment of arthritis, *Med Jr and Rec*, 1933, cxxlviii, 445-449
- 195 SLADEN, F J, ENSIGN, D C, and MCCOLL, C M Nutritional factors in chronic arthritis, *Proc Am Assoc, Study and Control Rheumatic Dis*, 1934, 34-40 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, ciii, 1734
- 196 PEMBERTON, R Some metabolic and nutritional aspects of chronic arthritis, *Am Jr Digest Dis and Nutrition*, 1934, i, 438-441
- 197 NISSEN, H A, and SPENCER, K A Sugar tolerance in the arthritic, *New England Jr Med*, 1934, ccv, 13-19
- 198 SNYDER, R G, TRAEGER, C H, FINEMAN, S, and ZOLL, C A Colonic stasis in chronic arthritis, *Arch Phys Therap*, 1933, xiv, 610-617
- 199 HARTSOCK, C The gastrointestinal tract in chronic atrophic (rheumatoid) arthritis, *Med Clin N Am*, 1934, xvi, 917-922
- 200 HOLZMAN, M B The value of diet in the treatment of arthritis and migraine, *Delaware State Med Jr*, 1933, v, 212-213
- 201 BOYD, E A The investigation of sweat in rheumatic subjects, *Irish Jr Med Sci*, 1934, s 6, 164-176
- 202 SULLIVAN, M X, and HESS, W C The cystine content of the finger nails in arthritis, *Jr Bone and Joint Surg*, 1934, xxxii, 185-188
- 203 SULLIVAN, M X Sulphur and cystine in relation to arthritis, *Med Ann District of Columbia*, 1934, iii, 233-236
- 204 WOLDENBERG, S C Sulphur (colloidal) therapy in the treatment of arthritis, *Med Rec*, 1934, cxxxix, 161-167
- 205 SENTURIA, B D Glutathione content of blood in chronic arthritis and rheumatoid conditions, *Jr Lab and Clin Med*, 1934, xix, 1151-1155
- 206 RUGH, J T Inflammatory joint conditions as affected by menstruation, *Am Jr Surg*, 1934, xxv, 126-130
- 207 IRONS, E E The treatment of chronic arthritis general principles, *Jr Am Med Assoc*, 1934, ciii, 1579-1583
- 208 IRONS, E E The new association and its purpose introductory remarks, *Proc Am Assoc Study and Control Rheumatic Dis*, 1934, 3-5 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1924, ciii, 1732
- 209 CECIL, R L Chronic arthritis—its treatment (part II), *Calif and West Med*, 1934, xli, 300-302
- 210 HOLBROOK, W P, and HILL, D F The management of atrophic arthritis in relation to the different phases of the disease, *Proc Am Assoc Study and Control Rheumatic Dis*, 1934, 78-87 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, ciii, 1802
- 211 DUCKER, A L Rheumatoid arthritis, with special reference to the arthritis clinic at the Royal North Shore Hospital of Sydney, *Med Jr Australia*, 1934, ii, 347-353
- 212 STEINDLER, A Focal infection and arthritis a statistical study, *Proc Am Assoc Study and Control of Rheumatic Dis*, 1934, 56-61 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, ciii, 1732
- 213 KEY, J A Discussion of paper by Steindler ²¹²
- 214 SOLIS-COHEN, M Necessity for revising the common conception of focal infection, *Jr Am Med Assoc*, 1934, cii, 1128-1131

- 215 SNYDER, R G, FINEMAN, S, and TRAEGER, C Importance of roentgenologic examination of the sinuses in chronic arthritis with special reference to cases in which the sinuses are a silent focus of infection, *Arch Otolaryngol*, 1934, xix, 23-39
- 216 GOLDFAIN, E The latest refinements in the vaccine treatment of arthritis, non-specific type, *Jr Oklahoma State Med Assoc*, 1933, xxvi, 361-364
- 217 MURPHY, L J A bacteriologic investigation of the arthritis and the preparation of an autogenous vaccine, *Illinois Med Jr*, 1934, lvi, 77-79
- 218 ROSS, G W Vaccine-therapy in chronic arthritis, *Canad Jr Med and Surg*, 1934, lxxv-lxxvi, 18-19
- 219 MARVIN, H P The value of intravenous vaccine therapy in arthritis, *Mil Surgeon*, 1933, lxxiii, 74-78
- 220 CARLSON, G W Chronic rheumatic diseases a study of 25 cases, with special reference to vaccine therapy, *Wisconsin Med Jr*, 1934, lxxviii, 481-484
- 221 NUTTER, J A, and WATSON, E R Chronic arthritis treated by Crowe's vaccine, *Canad Med Assoc Jr*, 1934, xxi, 34-38
- 222 NUTTER, J A Some reflections on arthritis, *Canad Med Assoc Jr*, 1934, xxi, 633-635
- 223 COHEN, A Chronic arthritis, *Med Rec*, 1934, cxxxix, 222-225
- 224 ROGERS, F L The use of vaccine in the treatment of chronic arthritis, *Nebraska Med Jr*, 1933, xviii, 427-431
- 225 WILLIAMSON, G A A synopsis of the treatment of chronic arthritis, *Physiotherapy Rev*, 1934, xiv, 14-17
- 226 GATEWOOD, W E, and HUNT, L W Arthritis its dietary treatment, *Northwest Med*, 1933, xxxii, 474-488
- 227 WHIFFLON, T The use of calcium ortho-iodoxybenzoate in the treatment of arthritis, with a discussion of its possible value in some other orthopedic condition, *ANN INT MED*, 1934, vii, 1540-1547
- 228 FORESTIER, J Rheumatoid arthritis and its treatment by gold salts, *Lancet*, 1934, ii, 646-648
- 229 SENTURIA, B D Results of treatment of chronic arthritis with colloidal sulphur, *Jr Bone and Joint Surg*, 1934, xxxii, 119-125
- 230 ARGY, W P Arthritis treatment with sulphur by intravenous and intramuscular injection, *Jr Bone and Joint Surg*, 1934, xxxii, 909-913
- 231 KLING, D H Treatment of myositis, arthritis and disturbances of the peripheral circulation with histamine by cataphoresis, *Arch Surg*, 1934, xxi, 138-148
- 232 KLING, D H Histamine therapy of rheumatic affections and disturbances of the peripheral circulation, *Ann Surg*, 1934, xci, 568-577
- 233 MACKENNA, F S The clinical application of histamine in rheumatism, *Lancet*, 1934, i, 1228-1229
- 234 KOVACS, R, and KOVACS, J Newer aspects of iontophoresis for arthritis and circulatory disturbances, *Arch Phys Therap*, 1934, xv, 593-598
- 235 COATES, V Modern methods in the treatment of chronic arthritis, *Practitioner*, 1933, cxxxix, 454-465
- 236 PERN, H The causation and treatment of arthritis and allied conditions, *Med Jr Australia*, 1934, ii, 179-186
- 237 HENCH, P S, and MEYERDING, H W The results of failure or neglect in the care of chronic infectious (atrophic) arthritis the characteristic deformities and their prevention, *Med Clin N Am*, 1934, xviii, 549-571
- 238 SWAIM, L T The orthopedic and physical therapeutic treatment of chronic arthritis, *Jr Am Med Assoc*, 1934, ciii, 1589-1594
- 239 McFEE, W D The relation of physical therapy to general practice, *Am Med*, 1934, xi, 37-42
- 240 GOERING, W H Physical therapy in chronic arthritis, *Physiotherapy Rev*, 1934, xiv, 24

- 241 WILATT, B L Paraffin treatment of chronic arthritis with special reference to an improved type of equipment, *Arch Phys Therap*, 1934, *xv*, 353-355
- 242 KOBAR, D Therapeutic heat, its technic and clinical evaluation, *Med Rec*, 1934, *cxi*, 250-254
- 243 BUCKLEY, C W Sub-thermal methods of treatment in rheumatic diseases, *Brit Jr Phys Med*, 1934, *ix*, 123-125
- 244 BUCKLEY, C W Physical methods in the treatment of rheumatism, arthritis, and fibrositis, *Practitioner*, 1935, *cxxxii*, 226-235
- 245 NADIG, A Fangotherapy in rheumatic diseases of motor apparatus, *Acta rheumatol*, 1934, *vi*, 47-49
- 246 HILL, L C Mineral waters in treatment of rheumatic diseases, *Brit Jr Phys Med*, 1934, *ix*, 125-127
- 247 LAUTMAN, M F Hydrotherapy in arthritis, *Arch Phys Therap*, 1934, *xv*, 107-110
- 248 WOLF, H F Physical therapy against protein shock in acute arthritis, *Am Med*, 1933, *xxxix*, 400-401
- 249 ROLLESTON, H Methods of physical treatment introduction, *Practitioner*, 1934, *cxxxii*, 129-131
- 250 MENNELL, J The manipulative treatment of disease, *Practitioner*, 1934, *cxxxii*, 166-179
- 251 CANTER, B M Manipulation of joints, *Internat Jr Med and Surg*, 1933, *xlvi*, 363-367, 372
- 252 COLLIE, J Medico-legal problems in general practice II Medico-legal aspects of physical medicine, *Practitioner*, 1934, *cxxxii*, 290-298
- 253 COPEMAN, W S C The treatment of rheumatism by physical methods, *Brit Jr Phys Med*, 1934, *ix*, 118-120
- 254 MACLURE, F Rest and movement, *Med Jr Australia*, 1934, *i*, 95-99
- 255 CUTTER, I S, and COULTER, J S The teaching of physical therapy to undergraduate medical students, *Jr Am Med Assoc*, 1934, *cii*, 1848-1850
- 256 KOVACS, R Physical therapy committees in state and county medical societies, *Jr Am Med Assoc*, 1934, *cii*, 1296-1297
- 257 COULTER, J S A plan for a registry of physical therapy technicians, *Arch Phys Therap*, 1934, *xv*, 234-236
- 258 NICHOLLS, E E, HANSSON, K G, and STAINSBY, W J Treatment of rheumatoid arthritis with hyperthermia produced by a high-frequency current, *Jr Bone and Joint Surg*, 1934, *xxxii*, 69-74
- 259 MARKSON, D E, and OSBORNE, S L Electropyrrexia in chronic infectious arthritis, *Arch Phys Therap*, 1934, *xv*, 167-171
- 260 MERRIMAN, J R, HOLMQUEST, H J, and OSBORNE, S L A new method of producing heat the inductotherm, *Am Jr Med Sci*, 1934, *clxxxvii*, 677-683
- 261 CURRENCE, J D Recent hydrotherapeutic observations in arthritis, *Arch Phys Therap*, 1934, *xv*, 490-491
- 262 MERRIMAN, J R, and OSBORNE, S L Hyperpyrexia, *Physiotherapy Rev*, 1933, *xiii*, 215-216
- 263 NEYMANN, C A, and OSBORNE, S L Physiology of electropyrrexia, *Am Jr Syph and Neurol*, 1934, *xviii*, 28-36
- 264 NEYMANN, C A, and OSBORNE, S L The development of hyperpyrexia, *Arch Phys Therap*, 1934, *xv*, 149-155
- 265 BIERMAN, W The effect of hyperpyrexia induced by radiation upon the leukocyte count, *Am Jr Med Sci* 1934, *clxxxvii*, 545-552
- 266 BIERMAN, W, and FISHBERG, E H Some physiologic changes during hyperpyrexia induced by physical means, *Jr Am Med Assoc*, 1934, *ciii*, 1354-1357
- 267 HOPKINS, H Chemical changes in blood induced by hyperpyrexial baths, *Arch Neurol and Psychiat*, 1934, *xxxix*, 597-604

- 268 MOEN, J K, MLDLS, G, and CHALEK, I The relative effects of diathermy and infection on plasma proteins, plasma viscosity and suspension stability of the blood in dogs, *Jr Lab and Clin Med*, 1934, xix, 571-581
- 269 KARR, J W, and NASSET, E S Physiological effects of high frequency current I The non-protein nitrogen partition and the secretion of urine in anesthetized dogs, *Am Jr Physiol*, 1934, cvii, 170-177
- 270 HOVERSON, E T A case of hyperpyrexia (110.5°) in artificial fever therapy, *Am Jr Med Sci*, 1933, cxlvi, 557-558
- 271 SHORT, C L, and BAUER, W Treatment of rheumatoid arthritis with fever induced by diathermy a follow-up study, *Jr Am Med Assoc*, 1935, civ, 2165-2168
- 272 HENCH, P S, STOCUMB, C H, and POPP, W C Fever therapy results for gonorrheal arthritis, chronic infectious (atrophic) arthritis, and other forms of "rheumatism," *Jr Am Med Assoc*, 1935, civ, 1779-1790
- 273 HENCH, P S Clinical notes on the results of fever therapy in different diseases (Report of the Fifth Fever Conference, Dayton, Ohio, May, 1935), *Proc Staff Meet, Mayo Clinic*, 1935, x, 662-666
- 274 WILLIAMSON, G A A synopsis of the treatment of chronic arthritis, *Physiotherapy Rev*, 1934, xiv, 14-17
- 275 BUSBY, B L Discussion of paper by Burbank¹⁴⁰
- 276 THOMSON, J E M Surgical possibilities of deformed arthritis, *Nebraska Med Jr*, 1933, xviii, 454-458
- 277 YOUNG, A Chronic rheumatism, *Trans Roy Med-Chir Soc*, 1933-1934, xxviii, 26-28
- 278 ROBERTSON, D E Sympathectomy in children, *Surg, Gynec and Obst*, 1934, lxi, 312-317
- 279 HOSFORD, J P Sympathectomy for chronic arthritis, *St Bartholomew's Hosp Rep*, 1933, lxvi, 33-35
- 280 BROWN, G E, CRAIG, W McK, and ADSON, A W The selection of cases of thromboangitis obliterans and other circulatory diseases of the extremities for sympathetic ganglionectomy, *Am Heart Jr*, 1934, x, 143-155
- 281 KUNTZ, A Sympathetic ganglions removed surgically a histopathologic study, *Arch Surg*, 1934, xxviii, 920-935
- 282 McMASTER, P E, and ROOMS, N W Experimental lumbar sympathectomy I Effects on vascular tree, reactive hyperemia and temperature of skin of extremities, *Arch Surg*, 1934, xxviii, 12-15
- 283 ROSENBLUETH, A, and CANNON, W B A further study of vasodilators in sympathectomized animals, *Am Jr Physiol*, 1934, cviii, 599-607
- 284 CLARK, S L A histologic study of the tissues of animals surviving complete exclusion of thoracic-lumbar autonomic impulses, *Jr Comp Neurol*, 1933, lviii, 553-591
- 285 CRAVEN, E B, JR Splenectomy in chronic arthritis associated with splenomegaly and leukopenia (Felty's syndrome), *Jr Am Med Assoc*, 1934, cx, 823-826
- 286 PRICE, A E, and SCHOENFELD, J B Felty's syndrome—report of a case with complete postmortem findings, *ANN INT MED*, 1934, vii, 1230-1239
- 287 SCHROCK, R D Fixation position for optimum joint function, *Nebraska Med Jr*, 1934, xix, 211-214
- 288 McBRIDE, E D The surgical treatment of arthritic joints, *Southwestern Med*, 1933, xvii, 321-323
- 289 GREEN, W T, and OBER, F R Chronic arthritis in children, *Proc Am Assoc, Study and Control of Rheumatic Dis*, 1934, 88-95 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, cxii, 1801-1802
- 290 HENCH, P S The analgesic effect of hepatitis and jaundice in chronic arthritis, fibrositis and sciatic pain, *ANN INT MED*, 1934, vii, 1278-1294
- 291 SIDEL, N, and ABRAMS, M I Jaundice in arthritis its analgesic action report of four cases, *New England Jr Med*, 1934, ccx, 181-182

- 292 KUHN, J G Hypertrophic arthritis of the hip review of 79 patients, New England Jr Med, 1934, cxx, 1213-1216
- 293 BICK, E M The pathogenesis of osteoarthritis, Acta rheumatol, 1934, vi, 4-9
- 294 GAMMON, J E Arthritis, Jr Florida Med Assoc, 1934, xxi, 53-57
- 295 DAWSON, M H Discussion of Steindler's paper²¹²
- 296 SCULL, C W, and PFMBERTON, R The influence of dietetic and other factors on the swelling of tissues in arthritis, Proc Am Assoc Study and Control Rheumatic Dis, 1934, 41-55 Also Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc, 1934, ciii, 1803
- 297 GOLDBERG, H Operation for bilateral osteo-arthritis of the hip Jr Bone and Joint Surg, 1934, vi, 721-723
- 298 KUHN, J G Chronic back strain a review of 100 cases treated conservatively, Physiotherapy Rev, 1934, xiv, 8-11
- 299 GOLDTHWAIT, J E Backache, New England Jr Med, 1933, cxc, 722-729
- 300 OWEN, W B Backache, South Med Jr, 1934, xxvii, 40-43
- 301 RUGH, J T Low back pain in adults, Pennsylvania Med Jr, 1933, xxxvii, 83-87
- 302 GHORMLEY, R K Low back pain with special reference to articular facets, with presentation of operative procedure, Jr Am Med Assoc, 1933, ci, 1773-1777
- 303 HAUSER, E D W Low back pain a new explanation of the pathogenesis and the treatment, Surg, Gynec and Obst, 1933, lvi, 380-384
- 304 JACKSON, R H Chronic sacroiliac sprain with attendant sciatica, Am Jr Surg, 1934, xxiv, 456-477
- 305 WEAVER, J B Some remarks on the narrowed lumbosacral disc as an etiological factor in "sciatica," Jr Kansas Med Soc, 1934, cxlv, 94-99
- 306 FREIBERG, A H, and VINKE, T H Sciatica and the sacro-iliac joint, Jr Bone and Joint Surg, 1934, xxxii, 126-136
- 307 FREEDMAN, E The behavior of the intervertebral disc in certain spine lesions, Radiology, 1934, xxii, 219-235
- 308 WENTWORTH, E T The history of backache, Physiotherapy Rev, 1934, xiv, 53-57
- 309 BUCKLEY, C W Diseases and injuries of the lower spine with special reference to compensation cases, Post-Grad Med Jr, 1934, x, 355-360
- 310 BURT, J B Some problems in the study of sciatica, Proc Roy Soc Med, 1934, xxviii, 73-77
- 311 YEOMANS, W Neuritis, sciatica and lumbago in old age, Brit Jr Phys Med, 1934, ix, 63-65
- 312 WOLF, H F Physical therapy of the sciatic syndrome, Arch Phys Therap, 1934, xv, 96-98
- 313 THOMSON, F G Treatment of pain in lumbago and sciatica, Practitioner, 1934, cxxxiii, 274-280
- 314 DOUTHWAITE, A H Evipan sodium in the manipulative treatment of sciatica, Brit Med Jr, 1933, ii, 1023-1024
- 315 MILLER, J L Chronic rheumatic diseases of the spine, Arch Int Med, 1934, liv, 161-169
- 316 DOUB, H P Chronic arthritis of the spine, Radiology, 1934, xxii, 147-152
- 317 KEEFER, C S, and MYERS, W K The incidence and pathogenesis of degenerative arthritis, Jr Am Med Assoc, 1934, cii, 811-813
- 318 ELY, L W Backache, lumbago, pain in lower part of the back, Arch Surg, 1933, xxvii, 189-202
- 319 BIGGARD, J D Arthritis of the spine with reference to nerve root symptoms, Jr Indiana Med Assoc, 1934, xxvii, 67-69
- 320 NACHLAS, I Pseudo-angina pectoris originating in the cervical spine, Jr Am Med Assoc, 1934, ciii, 323-325
- 321 VERNON, S Paralgnesia, paravertebral block for relief of pain, Am Jr Surg, 1933, xxi, 416-417

- 322 GHORMLEY, R K, and KIRALIN, B R The oblique view for demonstration of the articular facets in lumbosacral backache and sciatic pain, *Am Jr Roentgenol*, 1934, **xxxi**, 173-176
- 323 MITCHELL, C L Lumbosacral facetectomy for relief of sciatic pain case report, *Jr Bone and Joint Surg*, 1934, **vi**, 706-708
- 324 GREIG, D M Clinical studies in pathology of bone II Localized unilateral spondylitis, *Edinburgh Med Jr*, 1933, **xi**, 413-416
- 325 LICHTWITZ, L Gout, *Bull New York Acad Med*, 1934, **x**, 306-319
- 326 HENCH, P S Remarks on gout presentation of two cases, *Proc Staff Meet, Mayo Clinic*, 1933, **viii**, 717-719
- 327 LOCKIE, L M, and HUBBARD, R S Presentation of a case of gout, *Bull Med Soc County of Erie and Buffalo Acad Med*, 1934, **vi**, 10-12
- 328 LOCKIE, L M, and HUBBARD, R S Gout changes in symptoms and purin metabolism produced by high fat diets in four gouty patients, *Proc Am Assoc Study and Control Rheumatic Dis*, 1934, 96-106 Also *Proc Third Conference on Rheumatic Diseases, Jr Am Med Assoc*, 1934, **ciii**, 1883
- 329 JOHNSON, A S Arthritis as a possible manifestation of allergy to insulin, *New England Jr Med*, 1934, **ccxi**, 321-322
- 330 VINING, C W, and THOMSON, J G Gout and aleukemic leukemia in a boy aged five, *Arch Dis Child*, 1934, **ix**, 277-284
- 331 WEBER, F P Erythraemia with migraine, gout and intracardiac thrombosis, *Lancet*, 1934, **ii**, 808-809
- 332 EATON, E R, and LOVE, J Chronic arthritis The uric-acid relationship of chronic arthritis to the allergies, *Jr Am Inst Homeop*, 1934, **xxvii**, 269-274
- 333 COPEMAN, W S C Recent advances in the treatment of chronic rheumatism, *Practitioner*, 1934, **cxxxiii**, 459-465
- 334 STEIN, D, and MINNICH, W C Functional studies of patients on antiarthritic medication, *Jr Lab and Clin Med*, 1933, **xix**, 24-39
- 335 QUICK, A J The probable allergic nature of cinchophen poisoning with special reference to the Arthus phenomenon and with precautions to be followed in cinchophen administration, *Am Jr Med Sci*, 1934, **clxxxvii**, 115-121
- 336 SAYE, H Translation of a fourteenth century French manuscript dealing with treatment of gout, *Bull Inst Hist Med*, 1934, **ii**, 112-122
- 337 SCHLOTTHAUER, C F, and BOLLMAN, J L Spontaneous gout in turkeys, *Jr Am Vet Med Assoc*, 1934, **lxxxv**, 98-103
- 338 SCHLOTTHAUER, C F, and BOLLMAN, J L Experimental gout in turkeys, *Proc Staff Meet, Mayo Clinic*, 1934, **ix**, 560-561
- 339 QUICK, A J A new concept of the significance of uric acid in clinical medicine, *Med Clin North Am*, 1934, **xvii**, 1325-1337
- 340 QUICK, A J The relationship of uric acid excretion to ketosis, lactic acid metabolism, and aromatic acids, *Jr Biol Chem*, 1934, **cv**, 69-70
- 341 MARTIN, M F, and CORLEY, R G The excretion of allantoin and uric acid by the dog maintained on a purine-free diet, and on a protein-free diet The influence of the administration of glycine, *Jr Biol Chem*, 1934, **cv**, 57
- 342 GERSH, I Histochemical studies on mammalian kidney II The glomerular elimination of uric acid in the rabbit, *Anat Rec*, 1934, **lxiii**, 369-385
- 343 RANGANATHAN, S Attempts to produce uric acid calculi in albino rats, *Indian Jr Med Res*, 1934, **xxii**, 71-75
- 344 WALKER, A M Comparison of the chemical composition of aqueous humor, cerebrospinal fluid, lymph, and blood from frogs, higher animals, and man, reducing substances, inorganic phosphate, uric acid, urea, *Jr Biol Chem*, 1933, **ci**, 269-287
- 345 PRITHAM, G H, and ANDERSON, A K A comparison of methods for the determination of uric acid in human, bovine, and avian bloods, *Jr Lab and Clin Med*, 1934, **xix**, 892-896

- 346 BIRCH, C L Hemophilia, *Med Clin North Am*, 1933, vii, 351-368
- 347 BOGGS, R Spontaneous hemophilia Report of six cases in brothers, *Am Jr Med Sci*, 1934, clxxxviii, 811-815
- 348 FOULIS, M A, and CRAWFORD, J W Female "bleeders," *Brit Med Jr*, 1934, ii, 594
- 349 KAHN, M Hip joint changes in hemophilia, *Radiology*, 1934, xvii, 286-288
- 350 RUPINS, E L The roentgen-ray as an aid in the diagnosis of hemophilia, *Am Jr Roentgenol and Radium Therap*, 1934, xxxi, 597-602
- 351 SOLIS-COHEN, L, and LEVINE, S Bone and joint changes in hemophilia, *Am Jr Roentgenol and Radium Therap*, 1934, xxxi, 487-491
- 352 STETSON, R P, FORKNER, C E, CHEW, W B, and RICH, M L Negative effect of prolonged administration of ovarian substances in hemophilia, *Jr Am Med Assoc*, 1934, cii, 1122-1126
- 353 BREM, J, and LEOPOLD, J S Ovarian therapy relationship of the female sex hormone to hemophilia, *Jr Am Med Assoc*, 1934, cii, 200-202
- 354 TUREEN, L L Note on ineffective use of theelin in a case of hemophilia, *Am Jr Med Sci*, 1934, clxxxviii, 216-219
- 355 MCFARLANE, R G, and BARNETT, B The haemostatic possibilities of snake-venom, *Lancet*, 1934, ii, 985-987
- 356 KUGELMASS, I N Clinical control of chronic hemorrhagic states in childhood, *Jr Am Med Assoc*, 1934, cii, 204-210
- 357 SHARMA, B N A case of psoriasis of endocrine origin, *Indian Med Gaz*, 1934, lxi, 393-394
- 358 CAVADIAS, A P Metabolism in chronic rheumatics, *Acta rheumatol*, 1934, vi, 26-29
- 359 ANDERSON, C C Fibrositis causation and treatment, *Brit Jr Phys Med*, 1934, ix, 45-47
- 360 WARNER, E C Rheumatic disease in adults, *Lancet*, 1933, ii, 993-994
- 361 JONES, A B Reflections on aspects of rheumatism, *Am Med*, 1933, xxxix, 16-21
- 362 PENNINGTON, D Fibrositis a broad survey, *Brit Jr Phys Med*, 1934, ix, 120-123
- 363 ALBEE, F H Myofascitis, *Am Jr Surg*, 1934, xxiii, 70-78
- 364 ELSOM, J C Traumatic myositis, with hematoma and calcification, *Arch Phys Therap*, 1934, xv, 466-469
- 365 STOCKMAN, R Chronic rheumatism, *Trans Roy Med-Chir Soc*, 1933-1934, lxxviii, 13-15
- 366 McKEAG, P W Fibrositis and panniculitis, *Brit Jr Phys Med*, 1933, viii, 107-109
- 367 YOUNG, W Some methods of treatment in rheumatic affections, *New Zealand Med Jr*, 1934, xxxiii, 44-48
- 368 PICKLES, W N "Bornholm" disease account of a Yorkshire outbreak, *Brit Med Jr*, 1933, ii, 817-818
- 369 CRONE, N L, and CHAPMAN, E M Epidemic pleurodynia, *New England Jr Med*, 1933, ccix, 1007-1008
- 370 RICHTER, A B, and LEVINE, H D Epidemic pleurodynia, *Jr Am Med Assoc*, 1934, cii, 898-900
- 371 CALLAWAY, J L Epidemic pleurodynia, *South Med Jr*, 1934, lxxvii, 1019-1020
- 372 SNOKE, P O Myositis ossificans progressiva clinical notes and roentgen findings of a new case, *Am Jr Surg*, 1933, xli, 111-115
- 373 BURROW, H J Case of progressive myositis (fibrositis) ossificans, *Proc Roy Soc Med*, 1933, part 2, xxvi, 1330-1334
- 374 GWYNNE, F J, and ROBB, D Calcareous deposits in supraspinatus tendon and sub-acromial bursa, *Australian and New Zealand Jr Surg*, 1934, iv, 153-164
- 375 GROSSMAN, J Three hundred and seventy-five cases of periarthritis of the shoulder, with x-ray findings of 175, *Med Times and Long Island Med Jr*, 1933, lxi, 47-49
- 376 ROGERS, M H A study of 100 cases of subdeltoid bursitis, *Jr Bone and Joint Surg*, 1934, xli, 145-150

- 377 FRESCOLN, L D Care of the bursae, *Med Rec*, 1934, cxi, 10-11
- 378 EISING, E H Olccranon and prepatellar bursitis, *Med Rec*, 1934, cxi, 539-540
- 379 KAPLAN, E B Treatment of ganglion by injection of sodium morrhuate, *Am Jr Surg*, 1934, xxiv, 151
- 380 RAMAGE, J S, and MORTON, G B Two cases of iliopectoral bursitis, *Brit Jr Surg*, 1934, xxi, 705-708
- 381 BLACK, B M The prenatal incidence, structure and development of some human synovial bursae, *Anat Rec*, 1934, lx, 333-355
- 382 CHANDLER, S B Iliopsoas bursa in man, *Anat Rec*, 1934, lviii, 235-240
- 383 SUTTON, L P, and BOSWORTH, O Lymphatic leucemia resembling rheumatic fever in a child report of a case, *Jr Pediat*, 1934, v, 61-67
- 384 GHORMLEY, R K Lipoma of the capsule of the joint removed successfully presentation of three cases, *Minnesota Med*, 1934, xvi, 62-63
- 385 FERGUSON, A B Calcification in fat pads about joints, *Jr Bone and Joint Surg*, 1934, xvi, 418-422
- 386 JONES, E S Joint lubrication, *Lancet*, 1934, i, 1426-1427
- 387 KUHN, J G Lymphatic drainage of joints, *Arch Surg*, 1933, xlii, 345-391
- 388 KUHN, J G, and WEATHERFORD, H L The role of the reticulo-endothelial system, in the deposition of colloidal and particulate matter in articular cavities, *Proc Am Assoc Study and Control Rheumatic Dis*, 1934, 6-13 Also *Proc Third Conference on Rheumatic Diseases*, *Jr Am Med Assoc*, 1934, ciii, 1883
- 389 ELY, L W, and MENSOR, M C Studies on the immobilization of the normal joints, *Surg, Gynec and Obst*, 1933, lvi, 212-215

BOOKS 1934

The following books appeared during 1934 but are not reviewed herein

- 1 A short history of some common diseases (Includes chapter on rheumatism and arthritis) By divers authors Humphrey Milford, Oxford University Press, London, 1934, 211 pp
- 2 BRAILSFORD, JAMES F The radiology of bones and joints, 1934, Churchill, 520 pp
- 3 FOX, R F, and VAN BREEMEN, J Chronic rheumatism causation and treatment, J and A Churchill, Ltd, London, 1934, 364 pp
- 4 GADOW, H F The evolution of the vertebral column a contribution to the study of vertebrate phylogeny Edited by J F GASKELL and H L H GREEN, Macmillan, Cambridge University Press, 1934, 356 pp
- 5 KERSLEY, G D The rheumatic diseases a concise manual for the practitioner, William Heinemann, London, 1934, 88 pp
- 6 PEMBERTON, R, and OSGOOD, R B The medical and orthopedic management of chronic arthritis, Macmillan Company, New York, 1934, 403 pp
- 7 SYLVEST, E Epidemic myalgia Bornholm disease, with a foreword by Th Madsen Translated from Danish by Hans Andersen, Levin and Munksgaard, London, 1934, 155 pp

The chairman of the editorial committee for this review will welcome the receipt of reprints from authors of current (1935-1936) articles which will greatly facilitate the preparation of subsequent reviews

CASE REPORTS

VENTRICULAR COMPLEXES OF THE BUNDLE-BRANCH-BLOCK TYPE ASSOCIATED WITH SHORT P-R INTERVALS

By GEORGE H. ROBERTS, M D, F A C P, and DAVID I. ABRAMSON, M D,
Brooklyn, N Y

IN recent years a number of electrocardiograms have been reported possessing a shortened P-R interval and a bizarre, widened QRS complex of the type usually associated with an asynchronous activation of the two ventricles. Such cases have been described by Wilson,¹ Wedd,² Hamburger,³ Pezzi,⁴ Wolff, Parkinson and White,⁵ Holzmänn and Scherf,⁶ and Wolferth and Wood.⁷

The present report is concerned with an electrocardiographic study of a similar case with some further evidence relevant to the underlying mechanism.

CASE REPORT

A. N., a male, aged 44 years, a patent attorney by occupation, was seen by one of us in September 1932, following his rejection by an insurance company because of an abnormal electrocardiogram. Previously his only complaints referable to the heart were occasional attacks of palpitation since the age of six years, unassociated with effort or excitement, appearing suddenly, and lasting for a few minutes. During the attack his pulse was very rapid but regular, and he discovered early that he could terminate the palpitation by holding his breath.

Examination disclosed a well developed adult male. The heart was regular, rate 82, sounds were clear, and there were no murmurs, blood pressure 122 systolic and 80 diastolic. Fluoroscopic examination revealed the heart inclined transversely, but otherwise normal in contour and size.

Electrocardiographic Study. The first electrocardiogram, taken in September 1932, showed a normal sinus rhythm with a rate of 80 per minute. The P-waves were upright in all leads but very close to the ascending limb of the R-wave (P-R interval 0.12 sec). The QRS complex was widened, being 0.15 sec in duration and splintered at its apex. The terminal deflection was oppositely directed to the main deflection, the latter being upright in the three leads and similar to the type of complex seen in left bundle-branch-block (new classification) (Figure 1).

Despite an electrocardiogram usually associated with, and indicative of myocardial damage, it was thought, in view of the apparent good health of the patient, that the electrocardiographic alteration was not the result of organic involvement. Quinidine sulphate, gr. III q. i. d., was given for three days, and another record was taken. The latter showed a definite change from the first (figure 2, A). In all three leads, the abnormal complex had been replaced by normal R-waves associated with lengthened P-R intervals. Except for a left axis deviation, the electrocardiogram was normal in contour. Comparison of the two types of complexes revealed that the

* Received for publication July 18, 1935.

From the Department of Physiology and Pharmacology, Long Island College of Medicine, Brooklyn, N. Y.

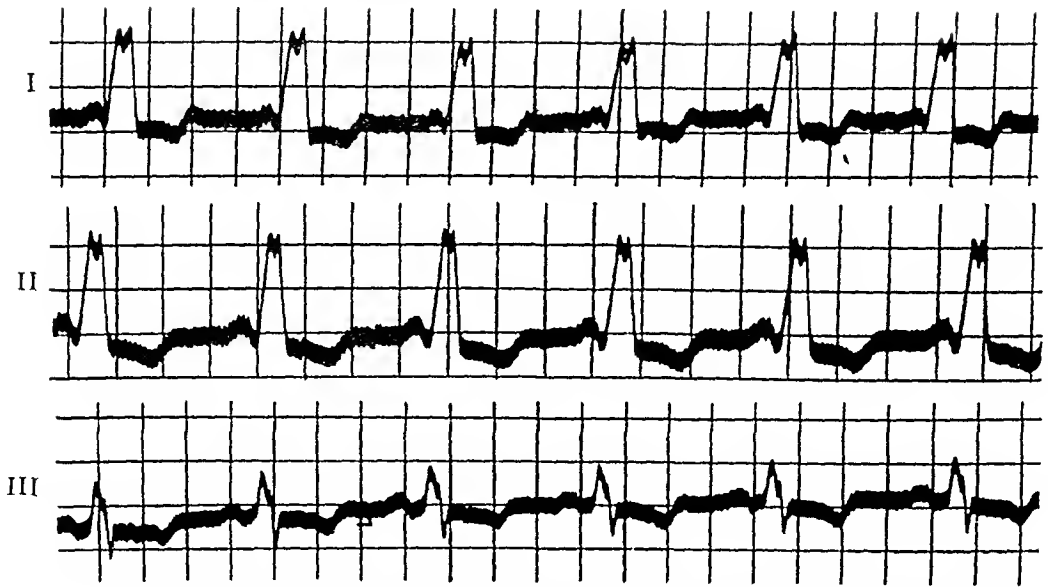


FIG 1 Usual type of electrocardiogram with short P-R interval and wide QRS complex.
Time, one-fifth second 1 cm = 1 millivolt



FIG 2 A Effect of quinidine medication—normal P-R interval and QRS complex present in the three leads

B Effect of subcutaneous injection of atropine sulphate, gr 1/50 Increase in heart rate noted with no change in contour of QRS complex

C Effect of digital pressure applied to carotid sinus Decrease in heart rate noted with no change in contour of QRS complex

distance from the beginning of P to the end of the QRS wave was approximately the same in both the normal and abnormal groupings (0.274 to 0.279 sec), and the contour of the P-wave was similar in both

In order to be certain that the changes recorded in the second tracing were not merely coincident with the quinidine medication, the latter was discontinued and one week later another electrocardiogram taken. This showed only the abnormal type

of QRS complex together with the short P-R interval. At two other periods, quinidine was again administered with approximately the same effect as in the above instance. The withdrawal of the drug always resulted in the return of the abnormal type of curve. At times without any treatment a spontaneous transition from the abnormal complex alone to alternate grouping of abnormal and normal complexes occurred (figure 3).

In the course of one examination the effects of exercise, digital pressure on the

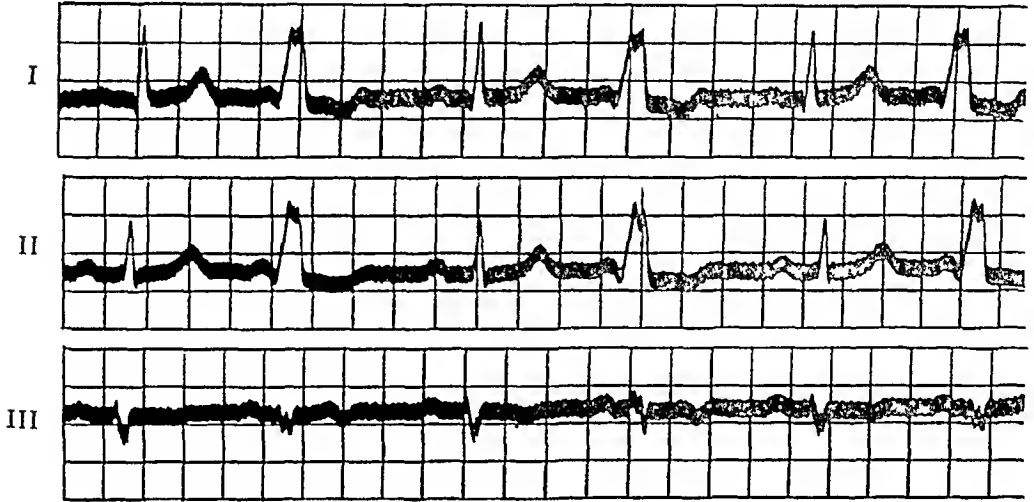


FIG 3 Electrocardiograms showing alternation of normal and abnormal groupings

carotid sinus and the subcutaneous injection of atropine sulphate were studied (figure 2, B and C). The rate decreased with carotid stimulation and increased after atropine and exercise. There was no change in the time relations and contour of the abnormal groupings. Electrocardiograms taken at intervals up to the present still reveal one or the other of the above states, but at no time except during quinidine medication have normal groupings been present more often than every other cycle. Unfortunately, no records were obtained during any of the attacks of paroxysmal tachycardia.

DISCUSSION

Twenty-eight cases possessing short P-R intervals associated with widened QRS complexes are described in the literature. The patients were all comparatively young and in only a few could an abnormal cardiovascular history be obtained. However, many had suffered from paroxysms of tachycardia, auricular fibrillation, or flutter.

Recently Wolferth and Wood reported nine such cases and reviewed the previous attempts to explain the mechanism. They further presented an hypothesis based upon the assumption that an aberrant conduction tissue connection (i.e., one besides the Bundle of His and its two branches) was present between the right auricle and right ventricle in these patients and that it was functionally able to conduct impulses. Such a structure has been described by Kent⁸ (Bundle of Kent), who presented histological evidence of the existence of a muscular connection between the right auricle and ventricle in the lateral wall. He demonstrated further that when all the structures which connect the auricles and

ventricles in a mammal are severed with the exception of this bridge of tissue, impulses still may be conducted from auricle to ventricle resulting in response of the latter

In some of Wolff, Parkinson and White's series, factors producing inhibition of vagal impulses brought about a transition to normal. Wolferth and Wood, and Holzmänn and Scherf found on the contrary no change under similar conditions. In our patient also, exercise, carotid sinus stimulation, and atropine had no effect upon the characteristics of the abnormal grouping. On the other hand subsequent to the administration of quinidine a normal electrocardiogram was obtained. This drug decreases the rate of impulse spread through conduction tissue as has been noted by numerous investigators, among them Cohn and Levy,⁹ Lewis,¹⁰ Schott,¹¹ Wolferth,¹² and Korns.¹³ If we assume therefore that the Bundle of Kent is able to conduct impulses in these patients (as have Wolferth and Wood, and Holzmänn and Scherf), a further assumption is reasonable that this tissue, which ordinarily does not have the properties of irritability and of conductivity as highly developed and as well stabilized as the Bundle of His, responds more markedly to depressants like quinidine. Following its administration the impulses tend to be conducted through normal channels. On withdrawal of the drug, the refractoriness of the Bundle of Kent again diminishes and impulses are conducted over it. Measurements made on the normal grouping over a period of three years consistently revealed a prolonged P-R interval (0.222 sec). Since such an increase is usually the result of a decreased rate of spread through the auriculo-ventricular node, it can be assumed that this is the explanation here. This may in part account for the fact that the effective impulse in most instances is the one traversing the aberrant pathway.

It seems likely that under these conditions the Bundle of His is able to conduct impulses and does so, but when the abnormal complex occurs, the conduction wave passes over two pathways: (1) via the Bundle of Kent, hence reaching the right ventricle prematurely, and (2) via the Bundle of His and its two branches. However, the impulse arriving at the right ventricle by way of the normal route (right branch) finds the ventricle already activated and therefore refractory. In the case of the left ventricle there is evidently a race between the impulses spreading down the left branch of the Bundle of His and those spreading across the septum from the prematurely activated right ventricle.

SUMMARY

An electrocardiographic study of a case is presented possessing ventricular complexes of the bundle-branch-block type associated with a very short P-R interval.

The effects of carotid sinus stimulation, exercise, atropine and quinidine upon the abnormal electrocardiogram are described.

REFERENCES

- 1 WILSON, F. N. A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram, *Arch. Int. Med.*, 1915, **vi**, 1008-1027.
- 2 WEDD, A. M. Paroxysmal tachycardia, *Arch. Int. Med.*, 1921, **xxvii**, 571-590.
- 3 HAMBURGER, W. W. Bundle branch block, *Med. Clin. N. Am.*, 1929, **xiii**, 343-362.
- 4 PEZZI, C. Considerations pathologiques sur quelques cas de rythme septal et para-septal permanents, *Arch. d. mal. du cœur*, 1931, **xxiv**, 1-24.

- 5 WOLFF, L, PARKINSON, J, and WHITE, P D Bundle-branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia, *Am Heart Jr*, 1930, *i*, 685-704
- 6 HOLZMANN, M, and SCHERF, D Über Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr f klin Med*, 1932, *cxxi*, 404-423
- 7 WOLFERTH, C C, and WOOD, F C Mechanism of production of short P-R intervals and prolonged QRS complexes in patients with presumably undamaged hearts, *Am Heart Jr*, 1933, *viii*, 297-311
- 8 KENT, A F S Observations on the auriculo-ventricular junction of the mammalian heart, *Quart Jr Exper Physiol*, 1914, *vii*, 193-195
- 9 COHN, A, and LEVI, R Experimental studies of the pharmacology of quinidine, *Proc Soc Exper Biol and Med*, 1921, *xxviii*, 283-284
- 10 LEWIS, T Actions of atropine and quinidine in fibrillation of auricles, *Am Jr Med Sci*, 1922, *clxix*, 1-14
- 11 SCHOTT, E Zur Frage der Chinidintherapie, *Deutsch Arch f klin Med*, 1920, *cxxxiv*, 208-218
- 12 WOLFERTH, C C Depression of cardiac conductivity during quinidine therapy, *Jr Am Med Assoc*, 1923, *lxviii*, 1289-1291
- 13 KORNS, H M Experimental and clinical study of quinidine sulphate, *Arch Int Med*, 1923, *xxxii*, 15-35, 36-55

EXCESSIVE SMOKING AS A POSSIBLE PRECIPITATING FACTOR IN DIABETIC GANGRENE, WITH A CASE REPORT *

By HARRY BLOTNER, M D, *Boston, Massachusetts*

TOBACCO smoking became of interest to me as a result of the work by Wright and Moffat¹ who found that smoking produced in the great majority of normal individuals a marked drop in the surface temperature at the tips of the fingers and toes, and frequently a slowing and stoppage of the blood flow in the capillaries of the nail fold. Shortly after their paper was published I saw a young man with diabetic gangrene who gave a long history of smoking a great many cigarettes each day. The case of this man is recorded to suggest that excessive smoking may be injudicious for the diabetic and even may be a factor in helping to precipitate fatal gangrene.

Mr S B was a Jewish business man, 34 years old. He entered the hospital on August 11, 1934, complaining of non-healing gangrene of the right foot. His family history was striking in that his mother died of diabetes at the age of 34 and a sister, now 29 years old, has had diabetes for several years. He had been married for six years and his wife and one child were living and well. He began to smoke at the age of 17 and used 30 to 40 cigarettes a day up to two years ago when he started to smoke more heavily. Since then he has smoked 40 to 80 cigarettes a day, a daily average of about sixty. For the past three years he has noticed at times on exertion numbness and tingling in his right leg. Three years ago he had weighed 223 pounds, but his weight had decreased to 150 pounds when he came under observation.

He was always well until 1931 when he began to feel easily fatigued and noticed that he was losing weight. His diabetic sister recognized the possible significance of these symptoms and got him to visit a doctor who confirmed the diagnosis of

* Received for publication June 20, 1935

From the Medical Clinic of the Peter Bent Brigham Hospital

diabetes At first the patient was treated with diet only, but after three months he began to take, in addition, 10 units of insulin three times a day, and for a year remained sugar free He then grew careless and omitted the insulin for a time, but his symptoms returned so that he resumed treatment

About eight months before entry to the hospital he began to have a noticeable amount of pain in the back of his right leg when walking At first the pain was trivial but as time went on it became more severe and more frequent Finally he could walk only for half a block before pain would compel him to stop He had no pain in bed at night

About four months before entering this hospital a small ulcer developed on the right little toe There was no history of any antecedent trauma He was then hospitalized elsewhere for 10 days and while in bed another ulcer appeared spontaneously on the sole of the right foot After this period of rest he got up and about and was able to walk a short distance with crutches The ulcers, however, failed to heal Four weeks before entry to this hospital he noticed that these ulcers had become black and foul with a purulent discharge and gradually they became so large and uncomfortable that he took to his bed, and entered our institution for treatment

His general examination was not remarkable except for evidence of loss of weight and gangrene of the right foot The blood pressure was 100 mm of mercury systolic and 60 diastolic

The Wassermann and Hinton tests were negative The hemoglobin was 94 per cent (Sahli), the red blood count 5,030,000, and the white blood count ranged from 25,000 to 13,000 The blood cholesterol was 185 and 140 mg on two occasions and the blood sugar varied from 276 mg to 160 mg The patient had rare insulin reactions, but no blood sugar determinations were made during them The urine was essentially negative and it seldom contained even the slightest possible trace of sugar even when the blood sugar was elevated

The radial arteries were not sclerotic but very soft and easily compressible The temporal and retinal arteries were normal The pulsations in the dorsalis pedis artery were present in the left foot but were absent in the right The popliteal pulse was felt on the left but not on the right The right foot showed swelling and redness on the lateral aspect The small toe was black On the sole of the foot there was an ulcerated area about 8 cm long and 4 to 6 cm wide over which the skin was black, crusted, indurated and somewhat peeling Beneath the crustation there was a foul purulent discharge Around this area of gangrene the skin was red, angry and edematous There was also a small ulcer over the external malleolus which was almost completely healed

Because of the patient's age there was doubt as to the underlying cause of the gangrene In the previous experience of this hospital diabetic gangrene has been encountered only once in so young a patient This was a man of 32 who developed gangrene apparently as the direct result of trauma and superimposed infection

At first it was thought that obliterative endarteritis (Buerger's disease) might be playing a part However, a number of tests were made which tended to exclude such a diagnosis Roentgen-rays of the feet, legs and thighs showed an osteomyelitis involving the distal end of the fifth metatarsal and the proximal end of the proximal phalanx of the right small toe In addition, there was marked calcification of the arteries of the feet and of the posterior tibial arteries of the legs up to the level of the proximal end of the fibula

Oscillometric studies of the arms and legs gave normal tracings over the arms and the left leg down to the lower part of the calf In contrast, on the right side there was decrease of the amplitude of the oscillations over the thigh and practically absence of oscillations from just above the knee downwards This indicated a very poor circulation on the affected side



FIG 1 Views of gangrenous foot of Mr S B, a diabetic patient

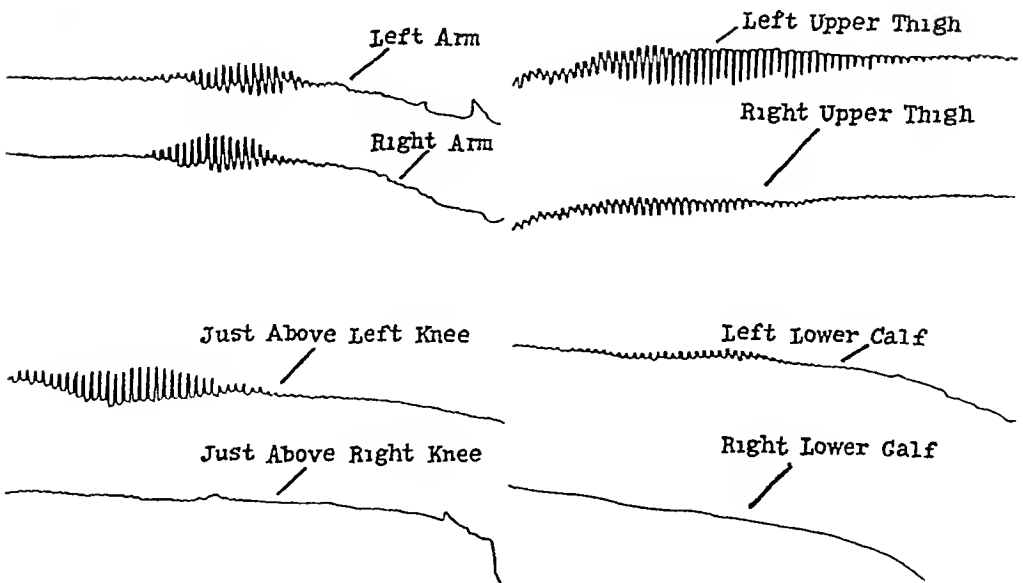


FIG 2 Oscillometric tracings of the arms and legs of a patient with diabetic gangrene, who smoked on an average of 60 cigarettes a day

Skin temperatures of the legs were determined with a thermocouple at frequent intervals during a control period until the temperatures remained constant and subsequently during a period of two and one-half hours while the patient was smoking cigarettes continuously. During all that time the patient lay flat in bed in a small room at a constant temperature. The temperature readings were taken at the tibial tubercle, the anterior ankle and the base of the great and small toes. Tobacco smoking produced a gradual decrease in the temperature at the various points during the

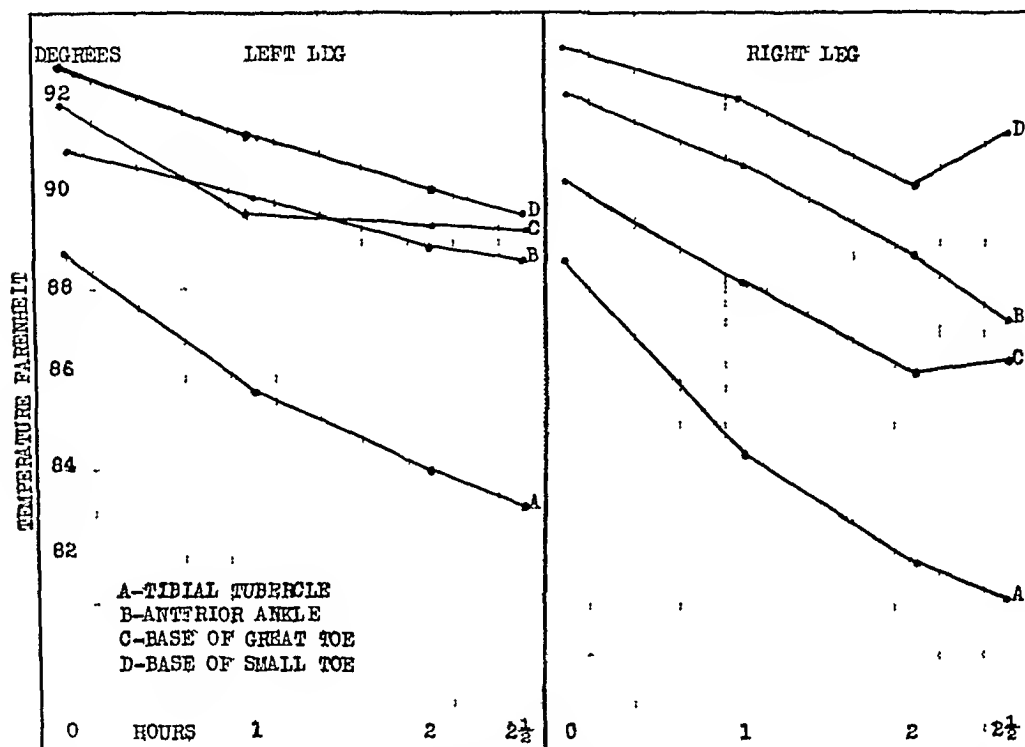


FIG 3 Skin temperatures of legs of Mr. S. B., a diabetic patient with gangrene of the right foot, while smoking cigarettes for 2½ hours

period of observation. The maximum drops in temperature occurred over the right and left tibial tubercles and these amounted to 7.1 and 5.3 degrees F respectively. The decrease in temperature at the other points was less striking. In Wright and Moffat's cases using tobacco, the average drop in skin temperature was 5.3 degrees F in one hour, the maximum drop was 15.5 degrees F. However, their experiments were conducted on normal individuals.

The patient was given a diet of 150 gm carbohydrate, 70 gm protein and 80 gm fat and 15 to 20 units of insulin three times a day before meals.

The leg was treated conservatively with a heat cradle and the wounds were kept clean. The foot improved and the toe became demarcated. However, in two weeks there developed suddenly a rise in temperature and some lymphangitis of the right leg. A mid-thigh amputation seemed indicated and was performed at once, and the patient progressed very satisfactorily until the ninth day postoperatively when the temperature again rose suddenly and the wound broke down and became infected. The infection progressed and invaded the subcutaneous tissues, producing necrosis of the fascia and muscle over the entire stump. Subsequent operations on the hip failed to be helpful and the patient died on October 10, 1934.

The essential pathological changes in the amputated leg consisted in a thrombosis of the posterior tibial artery. The clot filled the lumen of the vessel and extended from its origin to the region of the external malleolus. It was well organized and was evidently of long duration. Distal to the clot the plantar arteries and the peroneal artery showed considerable atheromatous change. The popliteal artery was not remarkable. Microscopic examination of sections from various parts of the arterial tree of the limb showed arteriosclerotic lesions of varying type. In some of the smaller vessels occasional fibrinous thrombi were encountered. However, the general picture was that of arteriosclerosis and not of thromboangitis obliterans.

The findings of the postmortem examination were otherwise irrelevant. There was extensive infection of the right hip and an abscess in the right side of the pelvis which extended around the rectum and was in direct connection with the muscles of the anterior thigh. Bronchopneumonia also was present in both lungs. The blood vessels in various organs and other parts of the body were in surprisingly good condition.

COMMENT

It is of practical interest to attempt to trace the etiology of the gangrene in this case. Certainly the fundamental lesion, as usual, was arteriosclerosis with superimposed thrombosis and infection. In line with the work of Wright and Moffat it is not unreasonable to suggest that the excessive use of tobacco by this patient may have been an important factor in precipitating the gangrene. The lowering of the skin temperature after the use of tobacco is thought to be caused by a slowing or stoppage of the circulation in the capillary bed. Such an effect in an extremity with an already diminished arterial blood supply may well play a considerable role in the early development of gangrene. Although the greatest drop in temperature observed after smoking was not more than 7.1 degrees Fahrenheit and hence not as marked as in some of the normal individuals used by Wright and Moffat, nevertheless it is possible that such a fall in temperature so induced, day in and day out over a long period of time in an individual with marked arteriosclerosis, was very harmful.

Since now it is known that the excessive use of tobacco produces definite effects on the peripheral vascular system, it will be of value in the future to investigate carefully the history of excessive smoking in diabetic patients. Diabetics who are ardent smokers should be advised moderation in smoking, since if they will avoid this deliberate insult to a peripheral circulation which already is likely to be diseased and easily vulnerable, they may thereby escape the vicissitudes of unnecessary gangrene.

REFERENCE

1. WRIGHT, I. S., and MOFFAT, D. The effects of tobacco on the peripheral vascular system, *Jr Am Med Assoc*, 1934, ciii, 318.

EDITORIAL

THE RÔLE OF THE LIVER IN HEMOPOIESIS

THE rôle of the liver in hemopoiesis has aroused increasing interest since the discovery by Minot and Murphy of the curative action of liver when fed to patients with pernicious anemia. It is now well established that liver contains some substance necessary for normal red cell production, which is produced in the normal body, but is lacking in pernicious anemia. A deficiency of this material results in an arrest of the maturation of the red blood cells and in the delivery into the blood stream of cells which are abnormal and functionally defective.

The work of Cohn et al., of West, and many others has shown that chemically this anti-anemic principle of liver is a relatively simple substance quite distinct from the vitamins, proteins and other nutrient materials present in liver. The development of methods of purification by Gansslen, and by various American workers, which permit intramuscular and even intravenous administration, is of great practical importance as well as of theoretical interest.

We owe to the work of Castle and his associates the first clear insight into the nature of the deficiency in pernicious anemia, as well as the source of the active substance. The action of some ferment-like constituent of normal gastric juice, the "intrinsic factor," on some substance present in certain foods (muscle meat, yeast, etc.), the "extrinsic factor," results in the production of a new substance which, after absorption by a patient with pernicious anemia, acts like liver extract in stimulating a reticulocyte crisis and a rapid production of red blood cells. The gastric juice of patients with pernicious anemia shows a lack (or a great reduction) of this intrinsic factor.

The fact that liver extract is also therapeutically effective in such diseases as tropical sprue, the "hemolytic" anemias of pregnancy and fish tape worm anemia, which show a macrocytic hyperchromic anemia morphologically similar to pernicious anemia, has led some to the generalization that macrocytosis is an indication of some disturbance in the production (or utilization) of this anti-anemic principle of liver. This assumption has received some apparent support from the observation of macrocytic anemia in some cases of advanced liver disease (Wintrobe and Shumacker,¹ Goldhamer et al.,² etc.).

Intensive study of these various diseases has shown that the conditions giving rise to the anemia may be complex. In some cases of sprue, the intrinsic factor is absent, as in pernicious anemia. In others the intrinsic

¹ WINTROBE, M. M., and SHUMACKER, H. S., JR. Occurrence of macrocytic anemia in association with disorders of the liver, *Bull. Johns Hopkins Hosp.* 1933 lii, 387.

² GOLDHAMER, S. M., ISAACS, R., and STURGIS, C. C. The rôle of the liver in hemopoiesis, *Am. Jr. Med. Sci.* 1934, clxxxviii, 193.

factor is present, and another explanation must be sought. In some cases of sprue and tropical anemia feeding large amounts of vegex or marmite (autolyzed yeast) relieves the anemia, and a lack of the extrinsic factor seems to be responsible for failure to form the active substance. In some cases of sprue, idiopathic steatorrhea, etc., deficient absorption seems to be the explanation. The intrinsic factor is present, oral administration of marmite or liver is uncertain in its effect, but parenteral injection of liver extract is highly effective.

In the case of anemia in disease of the liver, it is natural to assume that there is an inability of the liver to store, or possibly to elaborate the anti-anemic principle in a normal manner. There is considerable evidence that a defect of storage may exist. The intrinsic factor is probably not usually at fault. Achlorhydria is inconstant in these cases, and in one case¹ demonstration of the intrinsic factor in the stomach juice has been reported. Additional information of great interest has been obtained by a study of the content of anti-anemic principle in individual livers. By suitably preparing extracts of the liver of patients at autopsy, injecting them into patients with pernicious anemia, and observing the reticulocyte response, the presence or absence of the anti-anemic substance can be determined. This is regularly present in patients dying of unrelated diseases and in well treated cases of pernicious anemia in remission, but it is absent in untreated cases dying in an active stage of the disease. In some fatal cases of cirrhosis with macrocytic anemia, absence of the active principle in the liver has been demonstrated. Furthermore, parenteral injections of liver extract have relieved the anemia in some of the cases.

In one case of cirrhosis with anemia reported by Goldhamer et al the liver did contain the anti-anemic principle. The anemia in this case was attributed to an inability of the liver to mobilize the substance normally. Furthermore, Wilkinson and Israels² have reported a small series of cases of macrocytic anemia of unknown etiology whose gastric juice contained free acid, who showed no evidence of gross liver disease, who were not benefited by injections of liver extract, and whose livers contained the anti-anemic principle. They assume here an inability of the hemopoietic tissues to utilize the active principle, even when it is present in the body in adequate quantities.

Such conclusions are based largely on the assumption that because the anemia is macrocytic, it must be related in some way to a disturbance in the production or utilization of the anti-anemic principle of liver. However, as Minot has pointed out, anemia with macrocytosis occurs occasionally in a variety of diseases (leukemia, aplastic anemia, hemolytic jaundice) in which there is no evidence that this substance is involved, and it is quite possible that the macrocytic anemia of liver disease also is unrelated to it. Injections of liver extract are ineffective in some cases. As yet there are no adequate studies of the bone marrow.

² WILKINSON, J. F., and ISRAELS, M. C. G. Achrestic anemia, *Brit. Med. J.*, 1935, 1, 139, 194.

That the liver may play some part in the elaboration of the active material as well as in its storage is suggested by the fact that the active material as extracted from liver differs significantly from that in the gastrointestinal tract (and in "ventriculin") "Liver extract" is thermostable, it can be sterilized and is effective on parenteral injection. Its potency is increased by autolysis and by digestion with hog's stomach or normal gastric juice. The active material as it exists in the gastrointestinal tract cannot be extracted by the methods applicable to liver. It is destroyed by autolysis or prolonged digestion, it is thermolabile, and (except perhaps as "addisin") it has not been obtained in a potent form suitable for parenteral injection. There is, however, no direct proof that the liver is the site of this alteration, plausible as this appears. The change might occur in the intestinal mucosa during absorption. The fact that the material is stored in the liver does not prove that it is elaborated there. It is also abundant in kidney, and it is present in lesser concentration in other tissues (brain, placenta, etc.)

The study of these problems has been hampered by serious technical difficulties. The only available method (Castle's) for demonstrating the intrinsic factor is extremely cumbersome and quite impracticable except in large hospitals with an abundance of clinical material available. Demonstration of the active principle has been possible only by observing the response to it of untreated patients with pernicious anemia, who are now inconveniently rare. Hitherto the experimental production of the disease in animals has not been satisfactorily accomplished. Recent experimental work, however, offers hope that some of these difficulties may be eliminated. Thus Singer⁴ has reported a reticulocyte response in rats following injection of gastric juice containing intrinsic factor but negative responses with that from patients with pernicious anemia. Jacobson⁵ obtained a definite reticulocyte response in selected normal guinea pigs following the administration of active principle, and he has used this as a means of detecting and measuring the amount of the active principle. While quantitatively the responses reported are not impressive, his work receives confirmation from the observations of Miller and Rhoads,⁶ and it offers definite promise that animals will soon replace patients for this purpose.

Miller and Rhoads,⁷ utilizing swine because the gastric juice of these animals contains intrinsic factor, have recently produced a disease condition closely resembling tropical sprue and (less closely) pernicious anemia by feeding a diet similar to that by means of which Goldberger produced black tongue in dogs. These animals showed a severe anemia (usually

⁴ SINGER, K. Über eine tierexperimentelle Methode zum Nachweis des Castle-Prinzips des Magensaftes und deren klinische Bedeutung, *Klin. Wchnsch.*, 1935, *xiv*, 200.

⁵ JACOBSON, B. M. Response of guinea pig's reticulocytes to substances effective in pernicious anemia, *Jr. Clin. Invest.*, 1935, *xiv*, 679.

⁶ MILLER, D. K., and RHOADS, C. P. Reticulocyte response in guinea pigs following oral administration of certain anti-anemia substances, *New England Med. Jr.*, 1935, *ccxiii*, 99.

⁷ MILLER, D. K., and RHOADS, C. P. The experimental production of loss of hematopoietic elements of the gastric secretion and of the liver in swine with achlorhydria and anemia, *Jr. Clin. Invest.*, 1935, *xiv*, 153.

macrocytic), gastrointestinal disturbances with stomatitis, achlorhydria, loss of the intrinsic factor, disappearance of the active principle from the liver, and a hyperplastic megaloblastic bone marrow. The administration of liver extract caused a typical reticulocyte crisis, and clinical and hematological improvement. The possibilities for study which such experiments offer is obvious.

In summary, the only part played by the liver in erythropoiesis for which positive proof exists is that of a storehouse for the antianemic principle. The latter appears not to be an essential constituent of the liver cells. It is possible that the liver participates in the elaboration of the final product. It is also possible that a disturbance of its capacity to store or even to elaborate the active principle is responsible for the occasional development of macrocytic anemia in grave liver disease. That the liver may be found to exercise other important functions in the process of blood cell production is probable, but this is still pure speculation.

P W C

BOOK REVIEWS

Radium Treatment of Skin Diseases, New Growths, Diseases of the Eyes and Tonsils
By FRANCIS H WILLIAMS, M D 118 pages, 13 × 19 cm Stratford Company,
Boston 1935 Price, \$2 00

This is a delightful and simply written little book of one hundred and eighteen pages divided into three sections Part One consists of four chapters dealing with the nature and properties of radium and the use of radium in diseases of the skin and superficial new growths Part Two includes seven chapters dealing with radium in diseases of the eyes, and Part Three is made up of five chapters dealing with the treatment of tonsils and lymphoid tissues in the throat The twelve illustrations are simple and clear, although more illustrations could have been added to advantage

One of the attractive features of this book is its author—a pioneer in the field of radium therapy, who began his work in 1900, when little was known about the biological effect of radium and its usefulness as a therapeutic agent He was required to develop instruments to measure the penetration of tissues by the various rays in order to apply radium intelligently to clinical cases This meant detailed careful experimentations The book is a lasting record of Dr Williams' fundamental discoveries and is of real practical value

Parts Two and Three, dealing largely with clinical uses of radium in the specific fields covered by the book, are illustrated by typical cases, adding interest and clarity to the text The sphere of clinical use, of course, is limited, but the book is concise and valuable for a ready reference text

G E W

Classical Contributions to Obstetrics and Gynecology By HERBERT THOMS, M D ,
Associate Professor of Obstetrics and Gynecology, Yale University, and HOWARD
A KELLY, M D 265 pages, 15 × 23 5 cm Charles C Thomas, Springfield,
Illinois 1935 Price, \$4 00

In this book the author tells about the great specialists in women's diseases, beginning with Soranus of Ephesus who lived in the Second Century The contributions of any gynecologists or obstetricians now living have been omitted as has all material published since 1900 There has been no attempt to make this volume encyclopedial in type but rather the author has exercised the right of personal choice in selecting those men to write about who in his opinion have made the most important contributions to the development of gynecology and obstetrics

The general practitioner, as well as the specialist, will be glad to become better acquainted with the great obstetricians, who lived in the Eighteenth Century, among whom might be mentioned Mauriceau and Smellie but probably the most interesting part of the book is that which deals with the accomplishments of Charles White, Oliver Wendell Holmes, Semmelweiss and Pasteur, all of whom lived in the Nineteenth Century It is to these men that the human race should be always grateful for giving the medical profession a clearer understanding of puerperal infection

The last part of the book tells of the lives and achievements of those pioneers in pelvic surgery, who lived in the last Century, among whom we Americans are proud to claim as our own—Ephraim McDowell, Nathan Smith, Marion Sims and many others

Dr Thoms work should be of special interest to those who instruct medical students in obstetrics and diseases of women A little medical history interspersed through a lecture or clinic often adds interest, and the students through learning what

their forebears have accomplished in the struggle against disease may be stimulated to "carry on the torch"

L B

Gynecological and Obstetrical Tuberculosis By DR EDWIN M JAMESON, B S, Fellow of Trudeau Foundation, Attending Surgeon, Saranac Lake General Hospital and Reception Hospital 256 pages Lea and Febiger, Philadelphia 1935 Price, \$3 50

This monograph coming from the Trudeau Foundation should be of great interest not only to the gynecologist and obstetrician but also to the whole medical profession. The book is divided into three parts. The first deals with the alterations in the physiology of the female genital apparatus brought about by pulmonary tuberculosis. The second covers the various forms of female genital tuberculosis, while the third or last part of the book is given over to a discussion of the problem of pregnancy in the tuberculous woman.

The author has thoroughly reviewed the literature and there is a 36 page bibliography. However, what makes this monograph of such distinct value are the conclusions that Dr Jameson himself has reached, based on his own studies of the tremendous amount of clinical material available in the Trudeau Clinic. This is, indeed, a book well worth having.

L B

Pediatric Treatment By PHILIP S PORTER, M D 578 pages, 16 X 24 cm Macmillan Co, New York 1935 Price, \$5 00

The organization of material is excellent. Following the necessary basic review of general, local and emergency treatment, plus a chapter on pharmaceuticals, the diseases according to systems are then presented by a brief resume of clinical symptoms and signs with the therapeutic indications, followed by the therapeutics proper, under the subdivisions of general and symptomatic measures. Whenever prophylactic or quarantine measures are requisite they are described in the appropriate subdivision. Prescriptions are amply supplied and a final chapter consisting entirely of prescriptions of outstanding pediatricians is presented. The book is most complete, nearly every possible subject regardless of the value of treatment has been devoted space.

A therapeutic text almost uniformly reflects the climatological location of the author and likewise methods that are common usage in his (the author's) location. To the preceding, Dr Potter of California, is no exception, as may be evidenced by the statement on Page 220 (Treatment of Anorexia), "the child should be held upright after feeding and then taken out in the sunshine for an hour."

The author is a firm advocate of purging, even in many cases in which it would seem that this measure was of questionable value. The inclusion of practices in vogue elsewhere would have been a helpful addition to this volume.

The treatise is easily read. There is an excellent bibliography. It contains much of interest but cannot be said to constitute an advance over more familiar texts.

E B

Mouth Infection By OLIVER T OSBORNE, M D 119 pages, 14 X 21 cm 1934 Price, \$2 00

This book is an interesting treatise on the importance of mouth infection, its relationship to disease and the necessity for cooperation between physician and dentist in treatment. According to the author, many diseases, such as boils, neuritis, stomach and intestinal ulcers, endocrine disturbances, endocarditis, etc are often caused by oral infections.

In discussing devitalized or pulpless teeth, the author states that even when teeth are negative to roentgenographic examination, upon removal the *Streptococcus viridans* may be found within the root canal

Many case histories are included which are classed in several groups. With each history, there is a report of the oral examination. The reports of reexamination following medical and dental treatment reveal many interesting reactions.

The relationship of infected tonsils to systemic disorders is discussed and supplemented with actual case histories showing reactions following their removal.

Vincent's infection, its dangers and treatment are described.

The book closes with a discussion as to the possibility of the tooth brush, which is in general use today, causing continued reinfection of the mouth by being improperly kept.

The author's point of view is often stimulating even though his conclusions may not be fully supported.

B M D

PROGRAM
TWENTIETH ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
DETROIT, MICHIGAN

March 2-6, 1936

GENERAL SESSIONS

James Alex Miller, President

DETROIT COMMITTEES

Charles G Jennings,* General Chairman

COMMITTEE ON ARRANGEMENTS

C G Jennings,* Chairman	J D Bruce (Ann Arbor), Vice-Chairman
A F Jennings	H R Carstens
Thaddeus Walker	R C Jamieson
R H Stevens	W J Stapleton
F G Buesser	W A Evans

Mrs F W Hartman

COMMITTEE ON CLINICS

A F Jennings, Chairman
C C Sturgis, University Hospital, Ann Arbor
H A Freund, Harper Hospital
J T Watkins, Grace Hospital
F J Sladen, Henry Ford Hospital
B H Douglas, Herman Kiefer Hospital
T B Cooley, Children's Hospital
Douglas Donald, Receiving Hospital

COMMITTEE ON TRANSPORTATION

Thaddeus Walker, Chairman	
S W Wallace	A S DeWitt
A H Price	A D Holmes
C E Lemmon	P L Ledwidge
R A C Wollenberg	

COMMITTEE ON AUDITORIUM

R H Stevens, Chairman	
Lawrence Reynolds	F R Menagh
H A Luce	N J Whalen
R L Fisher	W H Gordon
W J Wilson	

* Deceased Jan 9, 1936

COMMITTEE ON PUBLICITY

F G Buesser, Chairman

R H Durham
R C Moehtig
C C Sturgis

W B Cooksey
H J Kullman
R L Schaefer

G L Waldbott

COMMITTEE ON ENTERTAINMENT

H R Carstens, Chairman

R M McKean
E D Spalding
J G Mateer

A P Biddle
Hugh Stalker
Douglas Donald.

C S Wilson

COMMITTEE ON ENTERTAINMENT OF VISITING WOMEN

Mrs F W Hartman, Chairman

Mrs F G Buesser
Mrs Douglas Donald
Mrs R H Durham
Mrs Hugo A Freund
Mrs A F Jennings
Mrs John G Mateer
Mrs R M McKean
Mrs Frank J Sladen
Mrs S W Wallace
Mrs John B Hartzell

Mrs Jesse T Harper
Mrs J Milton Robb
Mrs F C Kidner
Mrs Frederic Schreiber
Mrs H W Plaggemeyer
Mrs R C Jamieson
Mrs Wm J Stapleton
Mrs Hugh Stalker
Mrs James D Bruce
Mrs C C Sturgis

INVITATION

Detroit, one of the oldest of the large cities of the country and, in a sense, one of the newest, joins with Ann Arbor, the home of Michigan's great University, in extending for the second time a cordial invitation to the American College of Physicians to hold in these cities the Twentieth Annual Session of the College

The Michigan State Medical Society, the Wayne County Medical Society, the Detroit Academy of Medicine, the Medical Departments of the University of Michigan and Wayne University have, through their officers, assured the College of their hearty cooperation with the local committee to make the Session a success. The Department of Health and the Welfare Department with the wealth of clinical material under their control will give us their unqualified support.

The seven hospitals, at which will be given the clinical and demonstration programs, have a total bed capacity of 4051. The clinical amphitheatres and assembly rooms of these hospitals will accommodate 2000 persons.

Many distinguished clinicians from other cities of the United States and Canada will aid the local physicians, and this will give to the clinical program a truly cosmopolitan character.

The day in Ann Arbor will give to members the opportunity to visit the University of Michigan and to have a close-up view of the activities of its teaching hospital and laboratories.

The features of historic interest of older Detroit have been largely overgrown during the present century by its rapid rise to the position of the fourth city of the country in population and by the change in its character from a gracefully growing community to the greatest industrial city of the world.

While Detroit cannot rival the old cities of the East in structures and objects

GENERAL INFORMATION
HEADQUARTERS
BOOK-CADILLAC HOTEL
Washington Blvd

The Book-Cadillac Hotel will be not only the headquarters hotel for Officers, Regents, and Governors of the College, and so far as facilities permit, for members and guests, but also the general headquarters for registration, technical exhibits and all general scientific sessions

LIST OF DETROIT HOTELS

LIST OF DETROIT HOTELS			RATES PER DAY				
No of Rooms	Blocks Removed From Headquarters		Room—One Person		Room—Two Persons		Suites
			With Bath	Without Bath	With Bath	Without Bath	
1200		Book Cadillac, Washington Blvd	\$3 00-5 00		\$4 50-8 00		\$10 00-20 00
200	5	Briggs, 114 W Adams	2 00 up		3 00 up		
750	7	Detroit, Woodward & Adelaide	2 00 up	1 50 up	3 00 up	2 50 up	
800	3	Detroit Leland, Cass at Bagley	2 50 up		3 50 up		
900	3	Fort Shelby, Lafayette at First	2 00 up	1 50 up	3 00 up		
300	5	Madison Lenox, Madison & John R	2 00 up	1 25 up	2 50 up	2 00 up	
250	5	Norton, Jefferson & Griswold	1 50 up	1 25 up	2 50 up	2 00 up	
1000	3	Statler, Grand Circus Park	2 50 up		4 50 up		
800	3	Tuller, Park & Adams	2 00 up		3 50 up		
500	6	Wolverine, Witherell at Elizabeth	2 00 up		3 00 up		

of national historic interest, it can entertain its guests with the marvels of modern industrialism. It is the world's center of automobile production. Ninety per cent of the passenger car output of the country is made in the city and its environs. A visit to one of the great factories is an education in the methods of quantity production.

Belle Isle Park is one of the beauty spots of the city. Among the outstanding objects of interest are the Art Museum and Public Library at the Art Center, the unique American Museum at Greenfield Village at Dearborn and the Cranbrook School at Bloomfield Hills.

Since the Session of 1926 the hospitals of Detroit have doubled their capacity with modern buildings and equipment, and brought their laboratories and research departments to a high state of efficiency.

It is the hope of the local committees that their efforts will make the coming Session memorable for its educational value and for its enjoyable entertainment.

DIRECTORY

Headquarters	Book-Cadillac Hotel
Registration	Fourth Floor, Book-Cadillac Hotel
Technical Exhibits	Fourth Floor, Book-Cadillac Hotel
General Scientific Sessions	Ballroom, Book-Cadillac Hotel
Convocation	Ballroom, Book-Cadillac Hotel
Annual Banquet	Ballroom, Book-Cadillac Hotel

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1936 (dues, if not paid previously, may be paid at the Registration Bureau)
- (b) All newly elected members
- (c) Members of the Wayne and Washtenaw Counties Medical Societies, without registration fee, upon presentation of their 1936 membership cards
- (d) Medical students pursuing courses at the Wayne University, College of Medicine, and the University of Michigan Medical School, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions, exhibits and general sessions
- (e) House Officers of the hospitals participating in the program, upon presentation of proper identification, exhibits and general sessions
- (f) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials
- (g) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be open at the Book-Cadillac Hotel on Sunday afternoon and evening, March 1. The permanent Registration Bureau will be located on the fourth floor of the Book-Cadillac Hotel. Hours: 8:30 a.m. to 6:00 p.m., daily, March 2 to 6.

REGISTRATION BLANKS FOR ALL CLINICS AND DEMONSTRATIONS will be sent with the formal program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

THE CASHIER'S DESK at the Registration Bureau will receive payment of dues still delinquent, and accept orders for Banquet tickets, the College Key, the framed Fellowship Pledge, the Fellowship Certificate Frame and subscriptions to the ANNALS OF INTERNAL MEDICINE.

BULLETIN BOARD FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Book-Cadillac Hotel

TRANSPORTATION—Round trip tickets may be procured on the basis of one and one-third of the current one-way first class fares, with minimum excursion fare of \$1 00 for the round trip, upon presentation of identification certificates to be procured from the Executive Secretary of the American College of Physicians. The reduced fares apply for physicians and dependent members of their families.

Members are privileged to make the going journey by one route and return by another route. The fare for children of five and under twelve years of age will be one-half of the round trip fare for adults, children under five years of age free when accompanied by parents or guardian. Stop-overs will be allowed at all stations within final limit on either going or return trip, or both, upon application to conductors.

Before purchasing tickets, members must secure from the Executive Secretary an Identification Certificate, to entitle them to the reduced fares.

In general, tickets will be sold from February 19 to March 4, depending upon the relative distance from Detroit, with a return limit of thirty days in addition to date of sale.

All tickets must be validated by a special railroad agent at the Detroit Headquarters at the Book-Cadillac Hotel from March 2 to 6.

LOCAL TRANSPORTATION—Transportation to the University Hospital, Ann Arbor, on Wednesday, March 4, will be by buses. Fare for the round trip will be \$1 80. Tickets should be purchased at the desk near the Registration Bureau before 8 00 o'clock, Tuesday evening, in order that a sufficient number of buses will be available.

Buses will be stationed at the Book-Cadillac Hotel at 8 00 o'clock, Wednesday morning, and will start for Ann Arbor as rapidly as filled. Running time—1 hr., 20 min.

Street cars of the Hamilton Avenue line pass the Henry Ford and the Herman Kiefer Hospitals. These cars cross Washington Boulevard at Grand River Avenue, two blocks north of the Book-Cadillac Hotel. The Woodward Avenue cars going north pass within two blocks of Harper, The Grace and The Children's Hospitals.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5 30 p m., Thursday, March 5, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr Ernest B Bradley, Lexington, Kentucky.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A special dinner will be tendered to the Board of Governors by members of the Board of Regents at the Book-Cadillac Hotel, Sunday evening, March 1. An announcement of the time and place will be made later. Members of the Board of Governors are cordially invited.

COMMITTEE ON CREDENTIALS

Sunday, March 1, 10 00 a m

Parlor C, Fourth Floor, Book-Cadillac Hotel

BOARD OF REGENTS

Parlor C, Fourth Floor, Book-Cadillac Hotel

Sunday, March 1, 2 00 p m

Tuesday, March 3, 12 00 m *

Friday, March 6, 12 00 m *

BOARD OF GOVERNORS

Parlor C, Fourth Floor, Book-Cadillac Hotel

Monday, March 2, 5 00 p m

Wednesday, March 4, 12 00 m *

* *Buffet luncheon served*

SPECIAL FEATURES

MONDAY, MARCH 2, 1936

THE ANNUAL SMOKER will be given immediately following the scientific program, about 10 20 o'clock in the evening, in the Grand Ballroom of the Book-Cadillac Hotel. An unusual program of music and other entertainment will be given. Ladies are invited.

WEDNESDAY, MARCH 4, 1936

CONVOCATION OF THE COLLEGE—8 15 p m, Ballroom, Book-Cadillac Hotel. All Masters and Fellows of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in the Reception Room to the rear of the Grand Ballroom of the Book-Cadillac Hotel at 7 30 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Ballroom, to which they will be conducted by the Convocation marshal promptly at 8 15. As this is the most formal meeting of the College, it is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

Following the Convocation Ceremony, the President will present the John Phillips Memorial Medal for 1935-36. Thereafter will follow the Convocational Oration, "The Role of Emotion in Disease," by Dr. Walter B. Cannon, Professor of Physiology, Harvard University Medical School, Boston.

The President, Dr. James Alex. Miller, of New York City, will then deliver the annual presidential address, "The Changing Order in Medicine," to the Masters, Fellows and Associates of the College.

The Presidential Reception, in the Reception Room to the rear of the Grand Ballroom, will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception. All members and guests are invited to remain for dancing in the Grand Ballroom following the Reception.

THURSDAY, MARCH 5, 1936

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Grand Ballroom of the Book-Cadillac Hotel at 8 00 p m. All members of the College, physicians of Detroit and Ann Arbor and visitors attending the Session, with their families, are cordially invited to attend. Consult the banquet program to be printed later for announcement of the toastmaster and speakers.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The headquarters of the visiting ladies will be in the Founders Room on the fifth floor of the Book-Cadillac Hotel, near the Grand Ballroom.

The program for their entertainment has been arranged to give ample time for sightseeing, shopping and recreation. A folder giving points of interest, shops, theaters, concerts, etc., will be issued by the local committee.

ART CENTER—The Detroit Public Library and the Detroit Institute of Art, Woodward Avenue between Farnsworth and Kirby Streets. The Public Library contains the celebrated murals of Gari Melchers and the Art Institute the much discussed murals of Diego Rivera.

THE WAYNE COUNTY MEDICAL SOCIETY BUILDING 4421 Woodward Avenue. This is the meeting place of the medical men of the city and county. Its club features make it very popular both to members of the Society and the Women's Auxiliary, which has a large and active membership. An excellent restaurant serves luncheon and dinner at moderate prices.

Members of the College are cordially invited to visit the Society's home and inspect its work in the field of medical economies.

ANN ARBOR

LIBRARIES OF THE UNIVERSITY OF MICHIGAN contain about one million volumes, and include many notable collections. 6000 listed items of Greco-Egyptian papyrus, in size and importance surpassed only by the collections in London, Berlin and Cairo, a collection of Persian and Arabic manuscripts once owned by the Sultan Abdul Hamid, the Macmillan Shakespeare Library, 6525 volumes, the Parsons Library of Political Science, 6076 volumes, the Goethe Library 1131 volumes, the William L. Clements Library of American History with its collection of books, manuscripts, maps and newspapers relating to early American history.

THE LAW QUADRANGLE will be found of especial interest. It consists of the Lawyers' Club, the dormitories attached to the Club, the Legal Research building and the Law School building, Hutchins Hall.

THE MUSEUMS BUILDING houses the zoological, anthropological and paleontological collections of the University, including a number of important special collections, such as the Stevens Oriental Collection and the Chinese Government Exhibit from the New Orleans Exposition.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the fourth floor of the Book-Cadillac Hotel, on the way to registration and General Sessions.

Because of limitation of room and the impossibility of expanding the number of booths, many firms were unable to obtain space. Many of these firms have exhibited before the College previously, have established contacts among our members and would be in the exhibit again this year if possible. Among them are the following: The Doak Company, Cleveland, Kellogg Company, Battle Creek, Gradwohl School of Laboratory Technique, St. Louis, The Burdick Corporation, Milton Wis. Aznoe's National Physicians' Exchange, Chicago, Ayerst McKenna & Harrison Ltd., Montreal, The Battle Creek Food Company, Battle Creek, Ciba Company, New York, Spicer and Company, Glendale, Ernst Bisehoff Company, Inc., New York, S. H. Camp & Company, Jackson, Westinghouse X-Ray Company, Inc., Long Island City, Austin, Nichols & Co., Inc., "Vichy Celestins," Brooklyn.

However, the exhibit will be very representative, and will include medical literature and texts, pharmaceutical products, apparatus and appliances, and many other items of special interest to physicians, especially internists. These exhibits will afford an opportunity for physicians to keep informed of the latest literature and the newest products in the field of medicine generally, the educational value of these exhibits should not be overlooked. Furthermore the exhibitors contribute much not only to the interest of the meeting, but to the financial support of these scientific sessions. Every physician is urged to visit each of the booths, for he will certainly find something new, interesting and scientifically valuable. The exhibits will be closed on Wednesday, Ann Arbor Day. Special intermissions in the general program will be arranged, providing additional time for the inspection of exhibits.

TECHNICAL EXHIBITORS

AMERICAN COLLEGE OF PHYSICIANS

Detroit March 2-6, 1936

	<i>Space</i>
American Hospital Supply Corporation, Chicago, Ill	20
Appleton-Century Company, D, New York, N Y	55
Arlington Chemical Company, The, Yonkers, N Y	16
Bausch & Lomb Optical Co, Rochester, N Y	9
Becton, Dickinson & Co, Rutherford N J	10
Bilhuber-Knoll Corporation, Jersey City, N J	31-32
Burroughs Wellcome & Co (U S A), Inc, New York, N Y	34-35
Cambridge Instrument Co, New York N Y	28
Cameron's Surgical Specialty Co, Chicago, Ill	15
Collins, Inc, Warren E, Boston, Mass	25
Davies, Rose & Co, Ltd, Boston, Mass	40-41
Davis Company, F A, Philadelphia, Pa	53
Fischer & Co, H G, Chicago, Ill	50-51
Fougera and Co, Inc, E, New York, N Y	21
General Electric X-Ray Corporation, Chicago Ill	57-58-59
Gerber Products Co, Fremont, Mich	52
Lea & Febiger, Philadelphia, Pa	46
Lederle Laboratories, Inc, New York, N Y	29
Lippincott Company, J B, Philadelphia, Pa	27
M & R Dietetic Laboratories, Inc, Columbus, Ohio	8
Macmillan Co, The, New York, N Y	63
Maltine Company, The, New York, N Y	14
Mead Johnson & Company, Evansville, Ind	17-18
Medical Bureau, The, Chicago, Ill	47
Merck & Co, Inc, Rahway, N J	43-44-45
Merrell Company, The Wm S, Cincinnati, Ohio	54
Middlewest Instrument Company, Chicago, Ill	22
Morris & Co Ltd, Inc, Philip, New York, N Y	A
Mosby Company, The C V, St Louis, Mo	19
Oxford University Press, New York, N Y	62
Parke, Davis & Company, Detroit, Mich	1-2-3-4-5
Patch Company, The E L, Boston, Mass	23-24
Petrolagar Laboratories, Inc, Chicago, Ill	11
Ralston Purina Company, St Louis, Mo	33
Rare Chemicals, Inc, Nepera Park, N Y	36-37
Sanborn Company, Cambridge, Mass	49
Sandoz Chemical Works, Inc, New York, N Y	30
Saunders Company, W B, Philadelphia, Pa	48
Schering Corporation, Bloomfield, N J	26
Smith, Kline & French Laboratories, Philadelphia, Pa	6-7
Squibb & Sons, E R, New York, N Y	42
Taylor Instrument Companies, Rochester, N Y	12-13
Winthrop Chemical Company, Inc, New York, N Y	38-39
Wyeth & Brother, Inc, John, Philadelphia, Pa	60-61

GENERAL SESSIONS

In arranging the program for the General Sessions this year, an effort has been made to present a summary of the progress of medical knowledge in a few selected fields, and in carrying out this plan we are very fortunate to have secured the co-operation of outstanding leaders in various branches of medicine

This review plan of presentation will be followed in the consideration of the following diseases

Cardiac Disease, Diabetes, Virus Diseases, including Common Colds, Silicosis, Arthritis, and also the treatment of Pneumonia, of Pulmonary Tuberculosis and of Syphilis

In addition, the program contains special contributions to other phases of medicine

OUTLINE OF SESSION

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	March 2	March 3	March 4	March 5	March 6
9 00 a m to 12 00 m	Morning free Registration, Exhibits, etc	1st Clinical Session	" ANN ARBOR DAY " 2nd Clinical Session (beginning at 10 00)	3rd Clinical Session	4th Clinical Session
12 00 m to 2 00 p m	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2 00 p m to 5 30 p m	1st General Session	3rd General Session	5th General Session (finishing at 4 05)	6th General Session Annual Business Meeting	7th General Session
5 30 p m to 8 00 p m	Dinner	Dinner	Dinner		Dinner
8 00 p m to 10 00 p m	2nd General Session followed by Smoker	4th General Session	Convocation, followed by President's Reception and Dance	ANNUAL BANQUET	

Medical History—It has been thought desirable to include one paper upon this cultural subject as distinct from the purely clinical aspects of medicine

Neurology—The subject of the neuroses is considered from the standpoint of their causation and also of their treatment, and a very recent procedure of great value in the diagnosis and location of brain tumors will be described

Vascular Disturbances will be discussed from the standpoints of physiology and of hemodynamics

Diseases of Children—The subject of the use of convalescent serum in the treatment of acute infectious diseases, and also the treatment of the sequelae of birth injuries will be presented with the aid of motion pictures

Endocrinology—Some of the problems connected with the internal secretions, in addition to those of diabetes, will be discussed

Preventive Medicine and Public Health—In the presentation and discussion of both syphilis and silicosis, the preventive and public health aspects of these diseases will be emphasized

Medico-Dental Problems will be discussed both from the standpoint of medicine and of dentistry

The *Organs of Digestion* are considered in the discussion of certain conditions of the liver and of the intestines, including the treatment of constipation

Respiratory Diseases—In addition to the reviews of the treatment of pneumonia and of pulmonary tuberculosis, special phases of respiratory diseases, both tuberculous and non-tuberculous, will be presented

Experimental Studies of the Revived Human Heart will be presented in a fascinating manner by means of a motion picture

Ann Arbor Session—An unusual and unique feature of our program is the assignment of one entire day to the medical staff of the University of Michigan at Ann Arbor. The program for that day is very varied and promises to be of exceptional interest

The *Convocational Oration* will be delivered by Dr. Walter B. Cannon, Professor of Physiology at the Harvard University Medical School. This address will present a physiological approach to some of the important problems of medicine, under the title, "The Role of Emotion in Disease." Professor Cannon's reputation as a scientist and public speaker assures us of a most instructive and enjoyable evening. This address, as well as that of the President of the College, which will be delivered on the same evening, will contain much of general as well as of medical interest, so that it is hoped that many of our lay guests will find it both interesting and enjoyable to attend this session.

GENERAL SESSIONS

Ballroom, Book-Cadillac Hotel, Detroit, Mich

FIRST GENERAL SESSION

Monday afternoon, March 2, 1936

p.m.

2 00 Addresses of Welcome

CHARLES G. JENNINGS, General Chairman of the Twentieth Annual Session

GROVER C. PENBERTHY, President Michigan State Medical Society

ROBERT C. JAMIESON, President, Wayne County Medical Society

HENRY F. VAUGHAN, Commissioner of Health, City of Detroit

Response to Addresses of Welcome

JAMES ALEXANDER MILLER, President of the American College of Physicians

- 2 30 The History of Hospitals, with Special Reference to Some of the World's
Oldest Institutions
HENRY R CARSTENS, Detroit Mich
- 3 00 Viruses and the Diseases Caused by Them
THOMAS M RIVERS New York N Y
- 3 30 INTERMISSION
- 4 15 Recent Advances in the Study of Common Cold and Influenza
A R DOCHTZ, New York, N Y
- 4 45 Treatment of Birth Injuries and Allied Problems (Illustrated with Motion
Picture)
EARL R CARLSON, New York N Y
- 5 05 The Localization and Diagnosis of Tumors of the Brain by Olfactory Tests
CHARLES A EISENBERG New York N Y
- 5 35 ADJOURNMENT

SECOND GENERAL SESSION

Monday Evening March 2, 1936

Presiding Officer

JAMES E PAULLIN, Atlanta, Ga

p m

- 8 00 Diabetes Today and Tomorrow
ELLIOTT P JOSLIN, Boston, Mass
- 8 30 Disturbances of the Endocrine Balance and Their Relation to Diseases of
Metabolism
C N H LONG, Philadelphia, Pa
- 9 00 Ulcerative Conditions of the Small Intestine
PHILIP W BROWN and J DEJ PEMBERTON, Rochester, Minn
- 9 20 Use of Foods in the Treatment of Constipation
WILLIAM H OLMSTED, St Louis, Mo
- 9 40 Chronic Arthritis—A General Disease Requiring Individualized Treatment
ERNEST E IRONS, Chicago, Ill
- 10 00 ADJOURNMENT

10 20 o'Clock

SMOKER

Ballroom, Book-Cadillac Hotel

An unusual program of music and other entertainment has been arranged
Ladies are invited

Admission by registration badge

THIRD GENERAL SESSION

Tuesday Afternoon, March 3, 1936

 Presiding Officer

 ERNEST B BRADLEY, Lexington, Ky

p m

- 2 00 Errors in the Interpretation of Cardiovascular Symptoms and Signs
PAUL D WHITL, Boston, Mass
- 2 30 Errors in the Clinical Application of Electrocardiography
WILLIAM B BREED, Boston, Mass
- 2 55 Errors in Cardiovascular Roentgen-Ray Interpretation
HUGO ROESLER, Philadelphia, Pa
- 3 20 A Survey of the Newer Methods of Cardiac Therapy
WILLIAM D STROUD, Philadelphia, Pa
- 3 45 INTERMISSION
- 4 25 Studies of the Revived Human Heart (Motion Picture)
WILLIAM B KOUNTZ, St Louis, Mo
- 4 45 Some Factors in the Etiology of the Psychoneuroses
LOUIS CASAMAJOR, New York, N Y
- 5 15 The Treatment of Psychoneuroses
AUSTEN FOX RIGGS and HORACE K RICHARDSON, Stockbridge, Mass
- 5 45 ADJOURNMENT
-

FOURTH GENERAL SESSION

Tuesday Evening, March 3, 1936

 Presiding Officer

 WILLIAM J KERR, San Francisco, Calif

p m

- 8 00 The Public Health Control of Syphilis
THOMAS J PARRAN, JR, Albany, N Y
- 8 30 Modern Treatment Methods of Early Syphilis
JOSEPH EARLE MOORE, Baltimore, Md
- 9 00 The Prophylactic and Therapeutic Value of Convalescent Sera in Some of
the Acute Infectious Diseases
WILLIAM THALHIMER, New York, N Y
- 9 20 Medico-Dental Relations A Dentist's Viewpoint
J T O'ROURKE, Louisville, Ky
- 9 40 The Interrelations of Dentistry and Internal Medicine
SIDNEY R MILLER, Baltimore, Md
- 10 00 ADJOURNMENT

ANN ARBOR SESSION

Wednesday, March 4, 1936

The entire program, exclusive of the Convocation in the evening, will be conducted at the University of Michigan, Ann Arbor

FIFTH GENERAL SESSION

Wednesday Afternoon, March 4, 1936

Conducted by the Staff of the Department of Medicine of the University of Michigan
Ballroom of the University of Michigan Union

Presiding Officer

JAMES D. BRUCE, Ann Arbor, Mich

p.m.

- 2 00 Address of Welcome
ALEXANDER G. RUTHVEN, President of the University of Michigan
- 2 10 The Medical and Economic Advantages of an X-Ray Chest Survey of All
Hospital Admissions
FRED J. HODGES
- 2 35 Clinical Aspects of Water Balance and Dehydration
FREDERICK A. COILER
- 3 00 The Relation between Emotion and Disturbance of Physiologic Function
CARL D. CAMP
- 3 25 The Present Status of Pernicious Anemia, Experience with 600 Cases over
Eight Years
CYRUS C. STURGIS
- 3 50 The Surgical Treatment of Hypertension
MAX M. PEET
- 4 05 ADJOURNMENT

ANNUAL CONVOCATION

Wednesday Evening, March 4, 1936

8 15 o'clock

Ballroom, Book-Cadillac Hotel

The general profession and the general public are cordially invited. No special admission tickets will be required.

- 1 Convocation Ceremony
- 2 Presentation of the John Phillips Memorial Medal
- 3 Convocational Oration "The Role of Emotion in Disease"
WALTER B. CANNON, Professor of Physiology, Harvard University Medical
School, Boston, Mass

- 4 Presidential Address "The Changing Order in Medicine"
JAMES ALLAN MILLER, New York, N Y
-

President's Reception

Reception Room, Ballroom, Book-Cadillac Hotel

The Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

Dancing

SIXTH GENERAL SESSION

Thursday Afternoon, March 5, 1936

Presiding Officer

JAMES B. HERRICK, Chicago, Ill

p m

- 2 00 Clinical Manifestations and Studies in Parenchymatous Hepatitis
HUGO A. FREUND, Detroit, Mich
- 2 20 Treatment of Pneumonia
RUFUS I. COLE, New York, N Y
- 2 50 Adolescent Disturbances of Endocrine Function, the Importance of Their
Recognition and Treatment
CHARLES H. LAWRENCE, Boston, Mass
- 3 20 Vascular Physiology and Clinical Medicine
EUGENE M. LANDIS, Philadelphia, Pa
- 3 45 INTERMISSION
- 4 30 The Diagnosis of Silicosis with Special Reference to Roentgenologic Mani-
festations
LEROY U. GARDNER, Saranac Lake, N Y
- 4 50 Silicosis from the Public Health and Economic Viewpoint
A. J. LANZA, New York, N Y
- 5 10 Some Combinations of Certain Tuberculous and Non-Tuberculous Pulmonary
Lesions
F. MAURICE MCPHERDAN, Philadelphia, Pa
- 5 30 ADJOURNMENT

The *Annual General Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports from the Executive Secretary and Treasurer will be read, new Officers, Regents and Governors will be elected, and the President-Elect, Dr. Ernest B. Bradley, will be inducted into office.

Thursday Evening 8 00 o'Clock

Ballroom, Rook-Cadillac Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

SEVENTH GENERAL SESSION

Friday Afternoon March 6, 1936

Presiding Officer

GEORGE MORRIS PIERSON Philadelphia Pa

p m

- 2 00 Tuberculosis among Student Nurses, a Five-Year Study at Bellevue Hospital
J BURNS AMBERSON, JR., and H McLRON RICCINS New York N Y
- 2 20 The Present Status of the Treatment of Pulmonary Tuberculosis
LAWRASON BROWN Saranac Lake, N Y
- 2 50 Postural Pulmonary Emphysema
WILLIAM J KERR and JOHN B LAGEN, San Francisco, Calif
- 3 10 Clinical Problems of Hemodynamics in Nephritis and High Blood Pressure
ARTHUR R ELLIOTT, Chicago, Ill
- 3 30 INTERMISSION
- 4 15 The Lethal Effect of Solar Radiation on Guinea Pigs
MAX PINNER and ARON E MARGULIS, Oneonta, N Y
- 4 25 Acute Syphilitic Myocarditis—Simulating Myocardial Infarction, With a
Case Report
EDWARD C REIFENSTEIN, Syracuse, N Y
- 4 45 ADJOURNMENT

THE CLINIC SESSIONS

The program of the Clinic Sessions—from 9 00 a m to noon at Detroit (10 00 a m to noon at Ann Arbor)—has been modelled on those which have proved so successful in recent years. Emphasis has been placed on clinics in the true sense of the word, and there is scarcely a field of medicine which is not fully represented on the program. In addition to the various aspects of internal medicine, there are ample offerings in the subjects of pediatrics, psychiatry, neurology, roentgenology as well as in certain more distant fields which are still of importance to the internist, as for example bronchoscopy and certain surgical subjects. Ample opportunities in ward walks are offered for those who wish to see patients at close range and hospital methods in Detroit and Ann Arbor. Scientific demonstrations are offered on some programs that the visitors may see the research work actually being carried on at this time in the various laboratories.

The clinic program offers daily a capacity of over 2,000, scattered over six hospitals in Detroit and one in Ann Arbor. These hospitals are the following

- A Harper Hospital was opened for the care of patients on January 1, 1866. It has grown steadily until now it has a capacity of 625 beds caring for medical, surgical and obstetrical patients. Last year 13,478 patients received 117,376 days' hospitalization. It has well equipped pathological and x-ray departments and a large Outpatient Department Clinic with an average daily attendance of 294.
- B The Receiving Hospital is a city institution under the supervision of the Department of Public Welfare. It was opened in 1915 for the care of needy general hospital cases and the temporary detention of mental patients. In 1921 and again in 1927 notable additions were made to the hospital building. It now has a capacity of 650 beds.
- C The Henry Ford Hospital was incorporated under the laws of the State of Michigan on October 15, 1915. It is a general hospital with a bed capacity of 608, offering services to both in-patients and out-patients in all branches of medicine, surgery, pediatrics and obstetrics. In 1925 a school of nursing and hygiene was opened and operates in conjunction with the hospital.
- D The Grace Hospital was founded in 1888 by a group of public spirited citizens. In 1889 a Training School for Nurses was organized. A large Memorial Unit erected in 1931 increased the capacity to 529 beds. The hospital is a non-profit institution governed by an independent Board of Trustees. It cares for all forms of disease, except contagious and insane.
- E The Herman Kiefer Hospital, owned by the City of Detroit, controlled by the Board of Health. It has a capacity of 1,400 beds—services for all stages of tuberculosis in any form, contagious diseases, and maternity cases. A teaching hospital affiliated with the Wayne University, College of Medicine, houses the Department of Health Laboratories and the department's Outpatient Tuberculosis Clinics.
- F Children's Hospital of Michigan. The Children's Free Hospital Association was founded in 1886 by a group of Detroit women. In 1922 it was merged with the Michigan Hospital School, an organization for the care of crippled children, to form the Children's Hospital of Michigan. The city hospital with a capacity of 239 beds is for the care of acute medical and surgical patients. The hospital school, capacity 240 beds, is located in the country and is used as a convalescent home.
- G The Hospital of the University of Michigan opened in 1925 with a capacity of 825 beds, to increase the facilities of the old University Hospital which was built in 1869 and served as a teaching hospital for 56 years. There are now a total of 1,312 beds available for the care of the sick and for teaching, as well as ample provision for research.

The detailed programs at each of these hospitals are not printed herein. At the time this copy goes to press, it is too far in advance to name the actual cases that will be presented and to give the detailed titles of clinics and demonstrations. Furthermore, the full program of clinics and demonstrations would occupy too great space in this issue of the ANNALS. The official program, complete in all respects, will soon be distributed from the Executive Offices of the College.

COLLEGE NEWS NOTES

NOMINATIONS FOR ELECTIVE OFFICERS

The Committee on Nominations of The American College of Physicians, in accordance with the provisions of the By-Laws, presents the following nominations for the elective officers of the College for 1936-1937

President-Elect JAMES H. MANS, M D, Boston, Massachusetts
First Vice-President, O H. PERRY PIPPER, M D, Philadelphia, Pennsylvania
Second Vice-President, DAVID P. BARR, M D, Saint Louis, Missouri
Third Vice-President, WAITER L. BIRRING, M D, Des Moines, Iowa

Respectfully submitted

Committee on Nominations,
SIDNEY R. MILLER, Chairman,
FRANCIS M. POTTLENGER,
JAMES D. BRUCE,
ROBERT A. COOKE,
THOMAS KIRIN

NEW LIFE MEMBERS

Dr Willard J. Denno, New York City, and Dr Lewis B. Bates, Ancon, Canal Zone, Fellows of the College are new additions to the Life Membership Roster of the American College of Physicians

The Life Membership plan of the College is worthy of very careful consideration by each Fellow at this season of the year. The plan affords the member an opportunity of protecting his membership during his productive years and while his income is greatest, thus avoiding the burden of dues later in life. It provides for underwriting dues years in advance, but of receiving active membership throughout one's entire life. A member pays no more for Life Membership than he would pay for ordinary active membership to 65 years of age, without active membership thereafter, yet he receives active membership not only until 65, but for the balance of his life. Many members can readily afford Life Membership during their active, productive years, but, with changing conditions or ill health, find annual dues a burden in later life.

It is especially appealing to some members to take out Life Membership purely from an altruistic standpoint, namely, to make this contribution to the Endowment Fund of the College, putting the organization in position, financially, to broaden its activities along lines which are clearly suggested at this time, when there is so much conflict of thought and opinions on the subjects of medical practice, medical education, certification of specialists and other topics which are of primary interest to internists. Full details of the Life Membership plan, along with illustrations of the Life Membership Certificate, appear in the 1935 Directory of the College, pages 47 to 50.

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the following gifts to the College Library of publications by members

Fellows

Dr Malcolm T. MacEachern, Chicago, Ill—1 book, "Hospital Organization and Management"
Dr Walter A. Bastedo, New York, N. Y.—4 reprints
Dr Ralph O. Clock, New York, N. Y.—1 reprint

Lt Col George B Foster, Jr, (MC), U S Army—10 reprints
 Dr Benjamin H Frayser, Lexington, Ky—1 reprint
 Dr D Waldo Holt, Greensboro, N C—1 reprint
 Dr D O N Lindberg, Decatur, Ill—1 reprint
 Dr Harold C Ochsner, Waukegan, Ill—9 reprints
 Dr Henry A Rafsky, New York, N Y—7 reprints
 Dr William B Rawls, New York, N Y—1 reprint
 Dr Jesse D Riley, State Sanatorium, Ark—4 reprints
 Dr H C Robinson, Grand Rapids, Mich—1 reprint
 Dr Walter M Simpson, Dayton, Ohio—1 reprint
 Dr R Garfield Snyder, New York, N Y—3 reprints
 Dr Percy Harry Sprague, Edmonton, Alberta—6 reprints
 Dr August A Wernei, St Louis, Mo—3 reprints

Associates

Dr C Kelly Canelo, San Jose, Calif—2 reprints
 Dr Hyman I Goldstein, Camden, N J—3 reprints
 Dr W B Grayson, Little Rock, Ark—2 reprints
 Dr M Coleman Harris, New York, N Y—4 reprints and one book, "Normal Facts in Diagnosis"

CORRECTION TO 1935 DIRECTORY

Dr Charles Leonard Brown (Fellow), Philadelphia, is Professor of Medicine and Head of the Department of Medicine of Temple University School of Medicine, instead of Associate Professor of Internal Medicine, as printed in the new Directory

Dr Francis M Pottenger (Fellow) delivered the second Annual John W Bell Lecture on tuberculosis, at Minneapolis, December 2, 1935, under the auspices of the Hennepin County Tuberculosis Association and the Hennepin County Medical Society. Dr Pottenger's title was "The Responsibility of the General Practitioner in the Tuberculosis Program of the Future"

Dr A C Griffith (Fellow), Governor of the College for Missouri, was recently elected President of the Kansas City Southwestern Clinical Association

Dr Edward W Krumbhaar (Fellow) Philadelphia, and Dr Howard Dittrick, Cleveland, were appointed by the Department of State of the United States Government as delegates from the United States to the Tenth International Congress of the History of Medicine, at Madrid, September 23-29, 1935. They, with Dr Henry E Sigerist, Baltimore, also served as delegates of the American Association of the History of Medicine at the same Congress

Dr Joel J White (Fellow), Lieutenant Commander, has been selected for, and promoted to Commander, Medical Corps, U S Navy. Dr White has been detached from duty on the Staff of Commander Aircraft, Base Force, U S Fleet, based at San Diego, California, and assigned to duty with the Mayo Foundation, Rochester, Minnesota, for a special course in internal medicine

Dr Louis Faugeres Bishop, Jr (Fellow) presented a paper on "Recent Advances in Diagnosis and Treatment of Coronary Thrombosis" on November 20, 1935, at the meeting of the Southern Medical Association in St Louis. On the same day a paper on "A Report of Correspondence with Physicians in the Tropics on In-

vestigation of Coronary Thrombosis" was presented before the American Society of Tropical Medicine, St Louis, by Dr Louis Faugeres Bishop (Fellow) and Dr Louis Faugeres Bishop, Jr

Dr L D Sargent (Fellow), Washington, Pa, was elected Councilor of the Eleventh Pennsylvania District and a Censor of the Pennsylvania State Medical Society at its last annual meeting in October

Dr William Egbert Robertson (Fellow) was made President-Elect of the Philadelphia County Medical Society at its last annual meeting Dr Robertson is Emeritus Professor of the Theory and Practice of Clinical Medicine at the Temple University School of Medicine Dr Louis H Clerf (Fellow), Philadelphia, was elected Vice-President

Sir Aldo Castellani (Fellow), formerly Professor of Tropical Medicine of Tulane University of Louisiana School of Medicine, is supervising the Italian Medical Corps in Ethiopia

Dr Salvatore Lojacono (Fellow), Superintendent of Morgan Heights Sanatorium, Marquette, Michigan presented a paper on "Tuberculosis in Finns of Marquette County" at the November meeting of the Trudeau Society at Howell, Michigan

Dr John I Marker (Fellow) has been elected Vice-President of the Mississippi Valley Medical Society This Society covers the States of Illinois, Missouri and Iowa

Dr Fred C Oldenburg (Fellow), Cleveland, Ohio, was recently promoted to Assistant Clinical Professor of Medicine in the Western Reserve University School of Medicine

OBITUARIES

DR GEORGE ELGIE BROWN

George Elgie Brown of the Mayo Clinic, and Regent of the College for two terms (1929 to 1933), died in Rochester, Minnesota, November 28, 1935, after an illness of two weeks with pneumonia He is survived by his wife, Irma, and his mother, Mrs Ella Brown, also by a sister, Mrs Esther Frost, and two sons, George, Jr, a medical student at the University of Michigan, and Hugh, a student at Carleton College, Northfield, Minnesota

He was born in Grand Rapids, Michigan, July 16, 1885, and received his degree of Doctor of Medicine at the University of Michigan in 1909 He served an internship under the late Dr Walter Courtney at the Northern Pacific Hospital at Brainerd, Minnesota, and it was at Brainerd that he married Irma Parker July 22, 1911 Together they went to Miles City, Montana, where he engaged in an extremely active practice of general medicine, later developing internal medicine up to 1921 His interest in accurate scientific diagnoses was exemplified from the very first He was the first to develop in that part of Montana the complicated laboratory tests such as the Wassermann reaction, and introduced the first fluoroscope He

sought out special opportunities for clinical study, as well as extension of his knowledge in the basic sciences, as was shown by several months' study at Harvard in 1914 and at Johns Hopkins University in 1916. The war-time found him associated in France with the Rockefeller Foundation in 1918 and 1919.

Coming to the Mayo Clinic at Rochester, Minnesota, as First Assistant in medicine in 1921, he advanced rapidly in the Clinic and the Mayo Foundation (Graduate School of the University of Minnesota) to the position of Associate Professor of Medicine in 1927.

George Brown had a wide association and membership in the usual and especial medical societies. In addition to the local, county, state and national, he had membership in the American College of Physicians, American Society for Clinical Investigation, Association of American Physicians, American Association for the Advancement of Science, Central Interurban Clinical Club, Central Society for Clinical Research, Minnesota Society of Internal Medicine, Minnesota Heart Society, American Heart Association, Sigma Xi, and Phi Rho Sigma. In addition, he took an active interest, both as to attendance and program building, and was a prolific contributor—approximately one hundred and fifty articles in periodicals, systems of medicine and textbooks, and two monographs, and during his last illness and while sick in bed was working upon a number of manuscripts. His bibliography manifests the widest range of interest, as did his clinical interests and contacts, but in recent years he delved deeply into the problem of peripheral vascular disease, and in this field he became an international authority. At the time of his death he was working upon a monograph on vascular diseases and hypertension. He approached these problems evaluating the functional influence of the sympathetic nervous system, and his work is too well known to need further comment here.

He was gifted with a judicious balance of confidence in his own powers, with sufficient respect for traditional opinion, but not enough to insulate him against original thinking. This combination, fortified by a fine personal capacity to stimulate assistants and associates, led to his very productive years and the fullest utilization of his great opportunities, with the wealth of clinical material at the Mayo Clinic at his disposal. At the same time, while working as an original investigator, he was fully able to carry on as a clinician, to please and charm people, and give them the full benefit of his wide therapeutic experience. Never, however, did he lose sight of the duty he felt—to add all he could to the understanding of our medical problems. It is proverbial, in all walks of life, that many attain their ambitions by ruthless appropriation of the opportunities, the actual work, or the resources of others. Never could this be said of Dr. Brown. He beautifully exemplified the glory of our guild—the desire to share not only with humanity but with all of his fellows the best of his mind, his heart and personality. These powers helped him to become one of the best of traveling companions.

He was meticulous in his dress and personal appearance. He enjoyed relaxation, music, good food, stimulating reading, and he had a wide interest in world affairs.

It is thus, in his untimely passing, that his multitude of friends feel a crushing loss.

E. L. TUOHY, M.D., F.A.C.P.,
Governor for Minnesota

DR. LEWIS MANN SILVER

Dr. Lewis Mann Silver (Fellow), New York City, died August 14 of a fractured skull, as a result of a fall, aged seventy-five years.

Dr. Silver was born in Brooklyn in 1860, attended Phillips Academy at Andover, Mass., and was graduated from Yale University with the A.B. degree in 1882. He received his medical training at Bellevue Hospital Medical College, graduating in 1885. He did postgraduate work in Munich and Vienna. At the time of his death he was a member of the courtesy staff of the Babies' Hospital and assistant at the Vanderbilt Clinic of Columbia University College of Physicians and Surgeons. He was the author of a number of publications.

Dr. Silver belonged to the New York County Medical Society, the New York State Medical Society, the New York Academy of Medicine, the Medical Society of the Greater City of New York, the American Medical Association and the Society of Alumni of Bellevue Hospital. He had been a Fellow of the American College of Physicians since 1921. In addition to his medical societies, he was a member of the Yale Club, the Yale Alumni Association, the New England Society, the Vermont Society, the New Hampshire Society and the Sons of the Revolution.

ROBERT A. COOKE, M.D., F.A.C.P.
Governor for Eastern New York

DR. EDWARD W. JACKSON

Dr. Edward W. Jackson was born in Albion, N. Y., June 21, 1877, and died on October 2, 1935, in Rochester, New York, of his third cerebral hemorrhage.

Dr. Jackson graduated from Albany Medical School in 1907 and practised in Little Falls, N. Y., for three years. A severe automobile accident caused him to give up his work and after his recovery he devoted two years to study in various medical centers in Europe, notably in London with Drs. MacKenzie and Lewis. Returning to the United States he began the practice of cardiology and internal medicine in Rochester.

During the World War he served as Captain in the Medical Corps and acted as cardiologist at Camp Greenleaf and in Carlisle, Penna. After the war he resumed his work and continued as cardiologist and chief of the Heart Clinic at the Genesee Hospital, having first received his appointment

in 1913. He was a member of the state and county medical associations and of the A. M. A., the Rochester Academy of Medicine and was elected a fellow of the College of Physicians in 1924. He was a member of the Yonondio Lodge, F. and A. M. of the Damascus Temple, and the American Legion.

Cardiovascular disease forced him to give up his practice in Rochester, and during his latter years, his life was a long struggle with ill health. He went, successively, to California, Texas and Florida, attempting twice to resume a small amount of work in his specialty, but each time his reserve was insufficient, and he was forced to give up.

Dr. Jackson was a very earnest student of medicine and a man of tremendous capacity for work. His sympathetic and kindly nature endeared him to his patients to whom he gave his time and energy unstintedly, and thereby, no doubt, hastened his untimely death.

ROSCOE H. KNOWLTON, M.D., F.A.C.P.

DR. THOMAS CHALMERS

Dr. Thomas Chalmers (Fellow, 1919) deceased, November 16, 1935, was the son of an eminent New York physician, and a member of an old and important New York family. His mother was a Virginian of long American lineage and distinguished family.

Dr. Chalmers received his preliminary education in various private schools in and about New York City, and finally entered Princeton University, from which, however, he did not graduate. During his youth he was deeply interested in athletics, and took an active part in school and college work of this character. He graduated in medicine from Bellevue Hospital Medical College in 1897, substituted for a time on the Third Division of Bellevue Hospital, afterward serving in one of the out-patient departments of that institution.

In his youth Dr. Chalmers became a member of Company F of the Seventh Regiment of the New York National Guard, and remained with this organization at the time of the Spanish American War when he was transferred to the Twelfth Regiment of the New York National Guard as Captain and Assistant Surgeon. He served with this organization and on the Brigade Staff in Puerto Rico, and remained with the Army during the Philippine Wars, serving with distinction, and with the rank of Major, Medical Department.

On his return from the Philippine Islands, he again opened practice in West Ninth Street, New York City, where he remained until the formation of the colony at Forest Hills, Long Island, and he was one of the earliest physicians in this colony, and did much to establish a high standard of ethical and professional life in this part of Long Island.

Dr. Chalmers was actively interested in medical politics and for many years was a delegate to the American Medical Association. He was presi-

dent of the Queene County Medical Society, and was largely instrumental in the building of the Queene County Medical Building. He acted on numerous committees in connection with the health activities in this part of Long Island, and was a member of the New York Academy of Medicine, of the Advisory Council of the Commissioner of Hospitals, and on numerous other committees of professional organizations.

Dr. Chalmers married Miss Elizabeth Ducat on August 1, 1911. He was the father of three children.

Dr. Chalmers was well known for his high professional ability, his public spirit, his generous friendships, particularly to the younger members of the profession, and for his unswerving devotion to the highest standards of ethical medical practice. More than usual he possessed the power of attracting friends, both in and outside of his profession. Up to the very day of his death, he was actively engaged in public duties of many kinds beyond that which he gave to his own profession, and his patients. He was a fine citizen, a good soldier, and a high representative of his profession.

HARLOW BROOKS, M.D., F.A.C.P.

DR. ALEXANDER MCNIEL BLAIR

Dr. Alexander McNiel Blair was born in Buffalo, N. Y., July 30, 1873, and died at his home in Southern Pines, N. C., November 27, 1935.

Receiving his early education in the public schools of Buffalo and Niagara University, he graduated from the Medical Department of the University of Niagara in 1897. He settled in Southern Pines, N. C., in 1903, where he was actively engaged in practice save for the summer months, which he spent in Bethlehem, N. H., also in active work. His postgraduate work was done at Harvard University, Polyclinic Postgraduate Hospital in Philadelphia, Children's Hospital in Boston, and the Royal Victoria Hospital in Montreal. He was a member of the Volunteer Medical Service Corps during the World War, and at the time of his death was a member of the staff of the Lee County Hospital, Sanford, N. C. He became a Fellow of the American College of Physicians in 1925, and in addition held membership in the Moore County Medical Society of which he was President, the N. C. State Medical Society, the Tri State Medical Society, and the Southern Medical Association, as well as being a Fellow of the American College of Radiology.

Dr. Blair was actively interested in social and civic matters in his community, was a director in the Citizens Bank & Trust Co., and a member of the Presbyterian Church. His chief medical interests were diseases of the chest and stomach, though his work was not entirely limited to these phases of internal medicine. At the time of his death, he was the oldest practitioner in service in Southern Pines.

C. H. COCKE, M.D., F.A.C.P.,
Governor for North Carolina

DR ALBERT EDWARD ROUSSEL

Albert Edward Roussel (Fellow) was born in Philadelphia, September 17, 1863. He attended public and private schools and also studied under private tutors, later passing entrance examinations, admitting him to Annapolis. In 1882 Dr. Roussel was graduated from the Jefferson Medical College of Philadelphia, he served as interne in the Philadelphia Orthopaedic Hospital and Infirmary for Nervous Diseases, 1882-83, interne, Philadelphia General Hospital, 1883-84, served as externe in neurology, Hospital de la Salpetriere, Paris, 1885-87, and as externe in internal medicine and venereal diseases, St. Louis Hospital, Paris, 1887-88.

In 1888 Dr. Roussel pursued postgraduate studies in neurology and internal medicine at Heidelberg, Berlin, London and Paris. Upon his return to America he was appointed lecturer in physical diagnosis, Medico-Chirurgical College (1889-90), he became Associate Professor of Medicine and Clinical Medicine in the same institution in 1900, a position which he held until the merger of the Medico-Chirurgical College and Hospital with the University of Pennsylvania in 1916. He was elected Assistant Professor of Medicine in the University of Pennsylvania Graduate School of Medicine in 1916, and in 1920 was elected Professor of Medicine, ably filling that chair until 1932, when he became Professor Emeritus.

Dr. Roussel had served as Visiting Physician to the Polyclinic and Howard Hospitals, and held the position of President of the Staff at the latter institution for a number of years. He was also Visiting Physician to the Eagleville Sanitarium and to the French Consulate and Foreign Benevolent Society of Philadelphia. During the World War he became a member of the Medical Advisory Board and Special Medical Examiner for the French Government for the State of Pennsylvania. In 1907 Dr. Roussel received from the Government of France, the decoration, Officer d'Academie, and in 1924 also that of Chevalier de la Legion d'Honneur, from the same source.

Dr. Roussel was an honored member of numerous medical organizations, e.g., the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, the Philadelphia Pediatric Society, the American Medical Association (Fellow), and the American Association for the Advancement of Science. He was President of the American Therapeutic Society in 1929, and First-Five-President of the Philadelphia Medical Club, and since 1916 a Fellow of the American College of Physicians. Dr. Roussel contributed a number of articles to current medical journals and he was the first to point out that Brill's disease and typhus fever were the same disease.

Dr. Roussel had an attractive personality and his presence would cast a shadow of dignity over any gathering of physicians. From personal observation, during frequent and more or less prolonged contacts, the writer is convinced that he had a clearly demonstrated ability for straight thinking.

and reliable clinical observation that enabled him to reach an accurate diagnosis. His services in the capacity of teacher were highly appreciated by the Board of Trustees of the University of Pennsylvania, as shown by the fact that upon being retired from his professional duties he was immediately made Emeritus Professor of Medicine. His career as a whole is destined to endure for a long time in the minds of his pupils and medical practitioners who sought his services as a consultant. The subject of this sketch was quite familiar with French medical literature, on which he drew freely while teaching his medical classes.

Dr Roussel was a member of the Board of Governors of the Penn Club, with which he was prominently connected during many years. He was fond of hunting and, exceedingly so, of fishing.

Dr Roussel is survived by his widow, Mrs Albert E Roussel, who was a Miss Finn, and belonged to a socially prominent family of Baltimore, a son, Albert E Roussel, Jr, and a daughter, Mrs J Graham French.

J M ANDERS, M D, M A C P,
Philadelphia, Pa

NOTES ON MEDICAL EDUCATION AND MEDICAL INSTITUTIONS IN MICHIGAN

THE approaching General Session of the American College of Physicians, which is to be held in Detroit and in Ann Arbor, will give to the members of the College an opportunity to acquaint themselves with the present status of medical education and of medical institutions in the two chief medical centers of the State of Michigan. This approaching event should, therefore, lend interest to the following brief sketch of the development of the schools of medicine and of the hospitals which will furnish the clinical features of the program.

The long and stormy history of the early settlements and trading posts in the wilderness which has since become the State of Michigan, punctuated by warfare between the white settlers and the Indians, and between the forces of the French, the English, and later the Americans, contains little that is pertinent to the later development of medical institutions. Though Detroit was settled over two hundred years ago, the great hospitals and schools now existing were all founded within the last century.

Yet, lest the medicine and surgery of those earlier pioneer days in the wilderness should be too readily considered as unimportant, it should suffice to recall that it was towards the close of this period (1822), when Michigan was still a Territory, that William Beaumont, a surgeon in the United States Army stationed in the post at Mackinac, began his long series of scientific observations and experiments on gastric function on the trapper, Alexis St. Martin, who had been left after recovery from a gunshot wound with a permanent gastric fistula. This classical investigation must be looked upon as Michigan's first great contribution to scientific medicine. It still ranks in world medical history as one of the major advances in our knowledge of human physiology.

The history of medical education in Michigan is essentially that of the development of the medical school of the University of Michigan at Ann Arbor and that of the various medical schools in Detroit which have been continued as the recently formed Wayne University College of Medicine.

During the era of proprietary medical colleges, small schools were organized at various times in Detroit and other cities of the state, but they were short lived and of little importance.

The University of Michigan Medical School opened its doors to students in 1850 at Ann Arbor, and in 1869 the Detroit Medical College was incorporated. For half a century a fusion of these institutions was under consideration. Ann Arbor, in those earlier years a small city, had limited clinical facilities and, although the medical school was outstanding in the quality of its preclinical departments, many medical men both in Ann Arbor and Detroit believed that medical education in Michigan would be advanced

by the attachment of the Detroit school, with large hospitals and a wealth of clinical material under its control, to the Medical Department of the University

From the early eighties a number of conferences took place between the faculties of the two colleges looking to an amalgamation. The last conference met with the Council on Medical Education of the American Medical Association in Detroit in 1916.

A plan of union was proposed by the Council which was accepted by the Regents of the University and the Trustees of the Detroit College. The entry of the United States into the World War arrested the negotiations and they were not resumed. After the war the University of Michigan built its great teaching hospital and it now has the clinical facilities necessary to give a well rounded medical education.

WAYNE UNIVERSITY COLLEGE OF MEDICINE

The first attempt to give systematic medical instruction in Detroit was the organization in 1864 of a preparatory medical school by the staff of Harper Hospital, which was then used by the Government as a hospital for wounded soldiers of the Civil War. The instruction was almost entirely

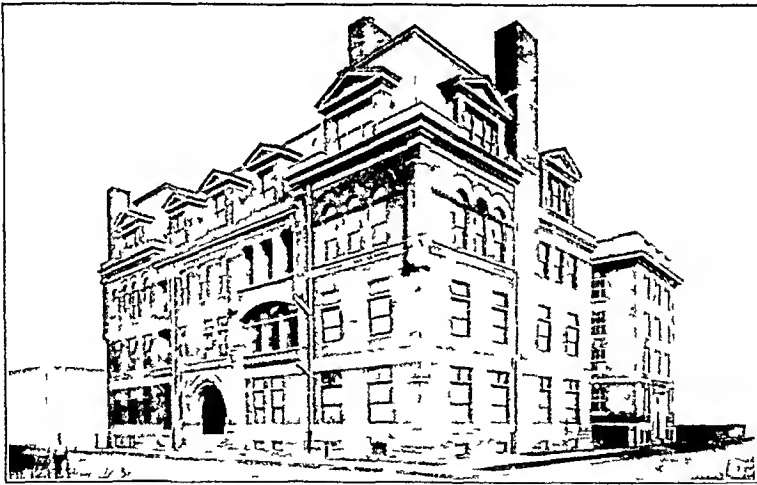


FIG 1 Wayne University College of Medicine

clinical. The venture was a success and in 1869 the school was expanded and incorporated as the Detroit Medical College, with a faculty of fourteen members.

Two of the pavilions of Harper Hospital were remodeled and made the college building. Harper and St. Mary's Hospitals, with a college out-patient department, furnished the material for clinical teaching. The success of the college and the professional advantage which a teaching position may give excited the envy of other medical men of the city. In 1879 a rival college, the Michigan College of Medicine, was organized and, after a stormy

period of competition, the two institutions amalgamated in 1882, under the name of the Detroit College of Medicine

The charter of the Detroit College of Medicine expired in 1913. Under a new charter and name, the Detroit College of Medicine and Surgery, the college was reorganized with faculty, equipment and curriculum brought up to modern requirements. The institution, however, did not have an adequate endowment and it had difficulty in maintaining the desired standard of medical education. In 1918, in order to save the college, its charter and property were taken over by the city. This ended its proprietary character and it became a unit of the public school system of Detroit under the control of the Board of Education.

The City of Detroit established Wayne University in 1933, and the medical college became the medical department of the University in 1934, under its present name, Wayne University College of Medicine.

Through all its changes in name and administration the present institution is a direct continuation of the Detroit Medical College organized in 1869.

The municipally owned Receiving Hospital and the Herman Kiefer Hospital, with a combined capacity of 2,050 beds, are the main teaching hospitals of the college.

THE RECEIVING HOSPITAL

The Receiving Hospital is operated by the City of Detroit and supervised by the Public Welfare Commission. It was founded in 1915 for the care of the indigent and emergency cases. It was re-organized in 1921 into a general hospital to include all services except obstetrics and contagious diseases, and was enlarged to its present capacity of 650 beds in 1927. The hospital still maintains a completely equipped emergency department supervised by the staff physicians. During 1934, 62,984 cases received treatment in the emergency room, 20,892 of which were subsequently hospitalized. These hospital admissions were distributed among the different services as follows:

General surgery	6564
Psychiatry	5653
Medicine	5252
Urology	1039
Gynecology	1609
EENT	1007

The hospital also maintains an out-patient department for the follow-up care of discharged patients, to which there were 106,692 visits during 1934. The hospital also houses the City Physician's Clinic which during 1934 had 368,239 visits. Much of this clinical material is utilized for teaching purposes.

The Receiving Hospital is the chief teaching unit of the Wayne University College of Medicine. Senior students serve as clinical clerks seven

hours daily for a total of twelve weeks in internal medicine, including psychiatry, neurology and dermatology, for four weeks in gynecology and for eight weeks in general surgery, including urology, orthopedics, and proctology. Junior students are taught physical diagnosis and pediatrics on the wards, and surgery and internal medicine in the out-patient department. Obstetrics and contagious diseases are taught at the Herman Kiefer Hospital.

THE HERMAN KIEFER HOSPITAL

The Herman Kiefer Hospital is a specialized institution, having services for all stages of tuberculosis in any form, all acute communicable diseases and maternity cases. There are 500 beds for contagion, 65 maternity beds and 65 bassinets, and 763 beds for tuberculosis. The institution is municipally owned and operated by the Board of Health.

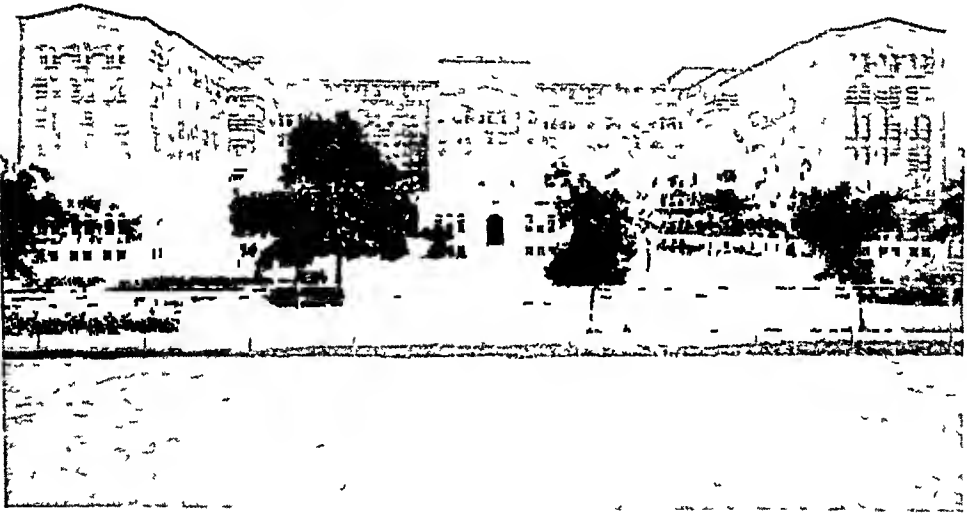


FIG 2 The Herman Kiefer Hospital

The contagious service is built on the unit, or pavilion plan, and the first building was erected in 1910. Construction of the new tuberculosis unit was begun in September 1927, and the building was opened for the reception of patients in December 1928.

This unit, with a capacity of 680 beds, is devoted to the care and treatment of tuberculous patients, who are admitted through the tuberculosis clinic of the Detroit Department of Health, housed in this building.

The structure is seven stories in height. On the first floor are the administrative offices, the social service department, library, record room,

physicians' offices, offices of the nursing executives, tuberculosis clinic and health department laboratories, as well as a modern and well equipped x-ray department

The second, third, fourth, fifth and sixth floors are devoted to the housing of patients. The rooms are either single rooms or for two patients, there being no wards, and most of them have porches. In fact, about 80 per cent of the patients can be placed on porches at one time. Each room, in addition to having prettily decorated furniture, is equipped with a radio head set. A microphone placed in the auditorium will enable speakers to give health talks to the whole patient population.

The surgical service occupies the entire seventh floor, excepting the wings, which are devoted to heliotherapy. There are five operating rooms, one of which has an amphitheater which seats 50 persons. Advances in the study and treatment of tuberculosis have brought forth corresponding advances in tuberculosis surgery, and the instrument, dressing and sterilizing rooms on this floor are equipped in the most up-to-date manner.

The space devoted to heliotherapy is divided into two sections, one side for women and the other for men. Each section is divided into compartments, one to be used for artificial sunlight and equipped with carbon arc lamps, and the other with an open roof for treatment by direct sunlight. Ultra-violet ray transmitting glass is also used in all of the patients' bedrooms.

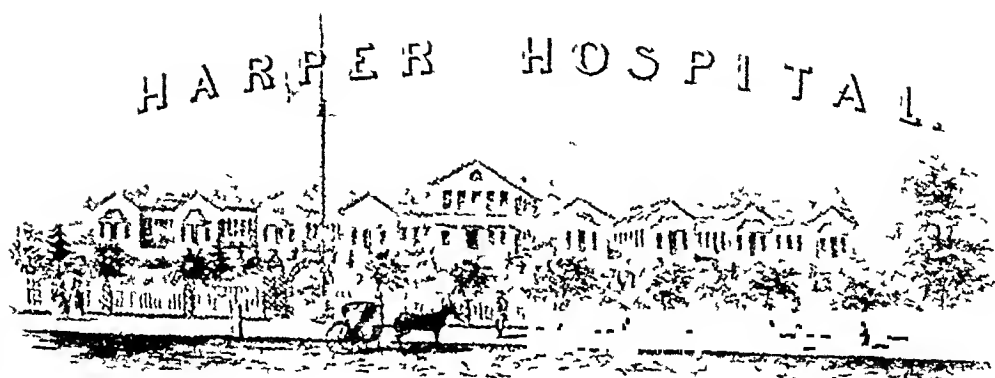
The value of the grounds, buildings and equipment is \$9,000,000.00. Operating expenses are in excess of one million dollars per year.

The hospital is a part of the teaching service of the Wayne University School of Medicine and affiliates with the various general hospitals in teaching their internes contagious diseases, tuberculosis and obstetrics. It also has a three-months' course in contagious diseases and tuberculosis for senior nurses, and has affiliations with 16 different hospitals.

In addition to the Wayne University College of Medicine and its two chief hospitals the members of the College will be interested in a number of other medical institutions in Detroit which will contribute valuable features to the program of the meeting.

HARPER HOSPITAL

Harper Hospital, one of the largest and oldest institutions in the city, was founded in 1859 through the generous gift of Walter Harper, whose name the hospital bears. At that time, an additional contribution was made by Nancy Martin, who gave a tract of five acres on Woodward Avenue (on which she had a market garden), together with other lands, to the new institution. During the Civil War, the Federal Government decided to establish a hospital for soldiers and sailors in the city, and the land was leased to the government for this purpose. The wooden buildings which



1864

FIG 3

were then erected housed the sick and wounded soldiers until 1865, when the buildings were turned over to the trustees, and the institution has been conducted as a general hospital ever since. In continuation of the tradition of war-time service, Base Hospital No. 17 was sponsored by Harper Hospital in 1917. It went overseas in July of that year, and was stationed in Dijon until 1919. This reserve unit has been continued as 17th General Hospital.

With growth of the city, and under the guidance of a Board of Trustees which has ever been keenly interested in medical progress, expansion followed, and in 1883 the new building (facing John R. Street) was completed. Later years saw the completion of many other units which were made possible by the generous gifts from citizens. In 1913, the Hudson Building (containing private rooms and wards), and the Buhl Building (housing the out-patient department) were completed. In 1918, a new operating pavilion was occupied, and 1928 saw the completion of the eight story building facing Brush Street.

The Fairland Training School for Nurses (one of the first established in this country) was opened in 1883, at first occupying the "Swain Home." As these quarters became inadequate, McLaughlin Hall was erected in 1921 to house the nursing staff and pupil nurses.

The laboratory, equipped for both routine work and research work, occupies the entire seventh floor of the center building. The department of roentgenology occupies extensive quarters on the first floor. Its equipment includes super-voltage therapy apparatus (700 K V. Constant), as well as experimental x-ray diffraction and neutron-ray apparatus.

The out-patient department was formally established in 1883, it outgrew its old quarters, and in 1914 occupied the new Buhl Building. About

10,000 to 12,000 new patients are treated yearly, the number of daily visits being 300 to 400

The hospital is completely equipped as a general hospital, and receives every type of case, excepting contagious diseases. It has a capacity of 625 beds, including private rooms and endowed ward beds

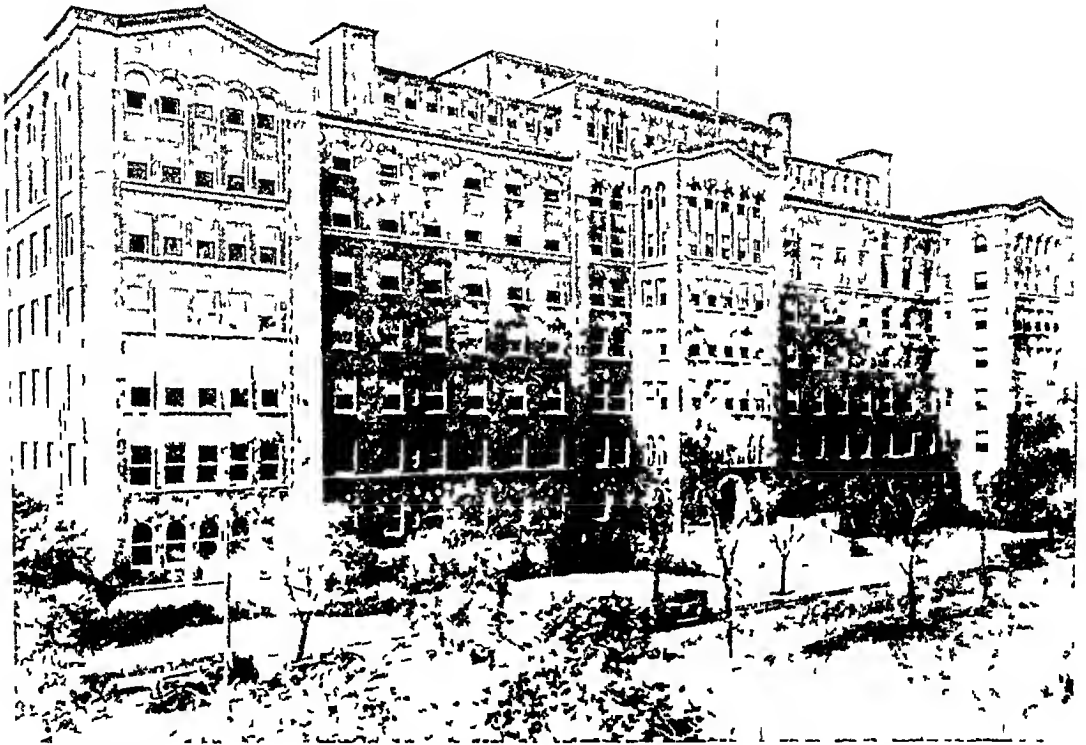


FIG 4 Harper Hospital Building erected in 1928

HENRY FORD HOSPITAL

In the year 1909 it became manifest to the medical profession and public-spirited citizens of Detroit, that the city's hospital facilities had not kept pace with the amazing progress made in other fields. There was then formed the "Detroit General Hospital Association" of which body Mr Henry Ford was a member, and of which he later became Chairman of the Board of Trustees. The purpose was the development of a hospital for Detroit under the name of the "Detroit General Hospital."

Two years later, namely, in 1911, ground was broken for the new institution and a building program begun. The work did not progress as was expected, so that with incompleting buildings, and with about one-third of the needed sum in hand, the original plan was enabled to continue only through Mr Ford's vision and generosity.

In June 1914, five years after the incorporation, and three years after the building program had begun, Mr Ford made an offer to take over full responsibility for the development of the new hospital. This offer was immediately accepted.

These chronological details tell the story of how the Henry Ford Hospital came into existence.

The Henry Ford Hospital was incorporated under the Laws of the State of Michigan on September 15, 1915. It is a general hospital with a bed capacity of 600, offering services to both in-patients and out-patients in all branches of medicine, surgery, pediatrics and obstetrics.

The hospital has been registering about 15,000 persons as patients a year. Recently the 227,300 mark was passed.

In 1925 a School of Nursing and Hygiene was opened and operated in conjunction with the hospital.

In the laboratories of the hospital facilities for research have been provided and from these laboratories as well as from the clinical departments a program of unusual interest may be expected.

THE GRACE HOSPITAL

The Grace Hospital was founded in 1888 by a group of public spirited citizens who contributed the cost of the original buildings and established an endowment fund of \$100,000, which was later increased to \$300,000. The site of the Hospital, at the corner of John R St and E Willis Ave, was contributed by one of the founders.

In 1910 an addition of four stories was built which included an x-ray suite, a group of operating rooms, a pediatric service, and a group of laboratories, together with accommodations for 50 additional private and semi-private patients.

The growth of the city soon placed added responsibilities on the Board of Trustees. In 1919, directly after the War, the Board instituted a construction program to cover a period of ten years and to involve the expenditure of \$2,500,000.

Between 1914 and 1930 the original Main Hospital Building on John R St was extensively reconstructed and improved. An obstetric ward and a urological unit were provided, and the roentgenologic equipment was modernized. In 1926 a third addition to the Main Hospital was built, which included an out-patient clinic service and 30 additional private rooms.

In 1929 a campaign for \$1,850,000 was carried through successfully for the purpose of increasing the bed accommodations in the main hospital, and as a result of this campaign the Memorial Building of the main hospital was constructed on the Brush St frontage.

In 1912 a member of the Board of Trustees donated a site and a building on West Grand Blvd, as a memorial to his deceased daughter. After alterations, 57 beds were provided, and thus a branch hospital, known as the

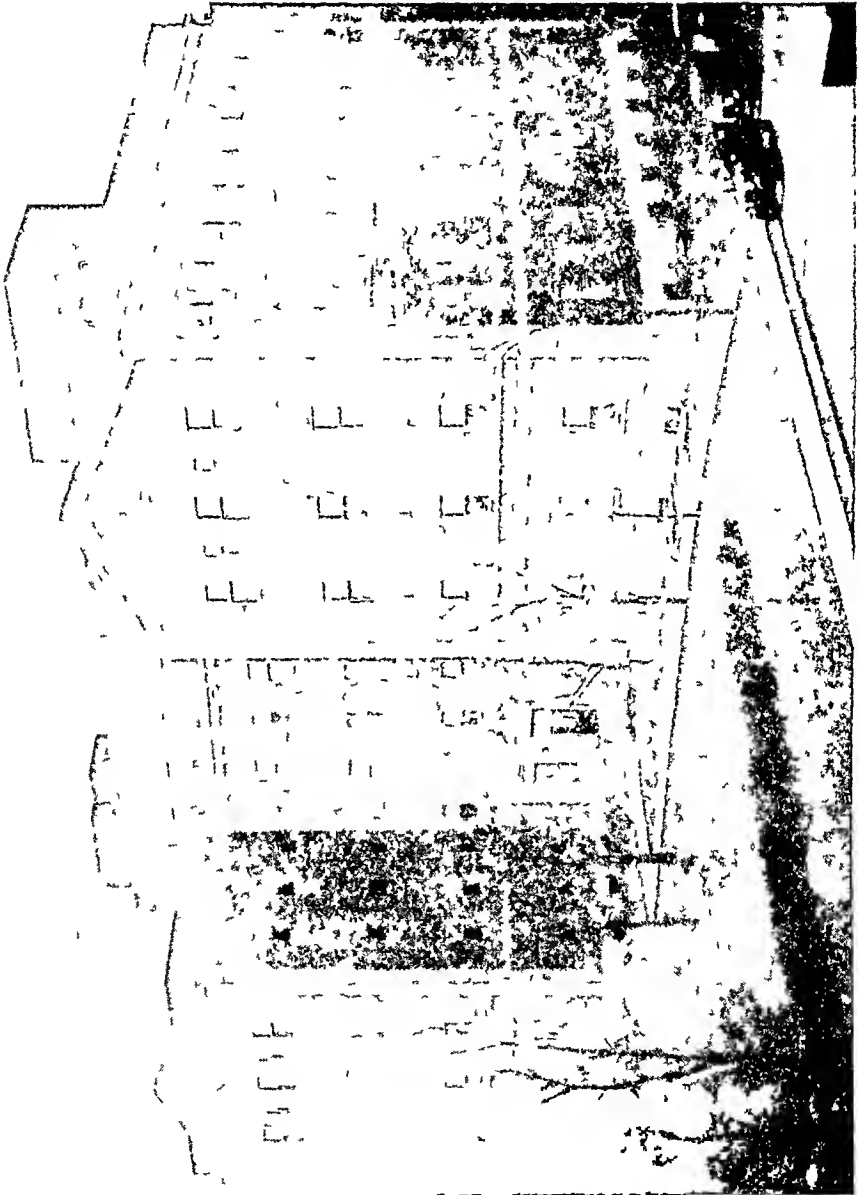


FIG 5 The Grace Hospital

Miriam Memorial Branch of the Grace Hospital, was opened, which has given a much needed community service to the West Side for many years

In 1919 a Nurses' Home for the Miriam Memorial Branch was built In 1929 the first unit of a new hospital building at this branch hospital was constructed

In 1889 the Training School for Nurses was organized and the first Nurses' Home, constructed later, was the gift of a public spirited woman

In 1931 a new Nurses' Home was erected at a cost of \$600,000 This addition was occupied first in 1932

The building of the new Nurses' Home permitted the expansion and improvement of the School of Nursing, with installation of modern pedagogic equipment The development of the Training School and the standards in nurse-teaching have kept pace with the growth of the Hospital

In the 47 years of its existence, the Hospital has cared for over 325,000 bed patients In 1935 the capacity of the Hospital was 527 beds In 47 years it has given relief to over 1,000,000 ambulatory indigents The cost of the latter has been partly provided by the Detroit Community Fund through the Council of Social Agencies

For more than two generations some of the leading representatives of the medical and surgical profession have served on the staff of this Hospital, and many of the prominent citizens of Detroit have been members of its Board of Trustees

CHILDREN'S HOSPITAL OF MICHIGAN

On November 12, 1886, a group of Detroit women who were interested in child welfare met and organized the Children's Free Hospital Association The first hospital work of this Association was begun on a ward in Harper Hospital Two years later, however, a temporary hospital was established in a house at Seventh and West Fort Streets In 1896 a generous gift from a prominent citizen of Detroit made possible the construction and endowment of the present building In 1922 a merger was effected with the Michigan Hospital School which possessed a building in the country at Farmington, and the merged institutions assumed the name of the Children's Hospital of Michigan This made it possible for the acute medical and surgical cases to be cared for in the city hospital, while the Hospital School building at Farmington was used as a convalescent home

Since this merger, many new facilities have been added New wings have been constructed to the main hospital and additional buildings have been erected at Farmington A nurses' home, a new out-patient department, a new roentgenologic department and new laboratories have all been added to the facilities of the city hospital The city branch now has a capacity of 239 beds and the country branch has 240 beds The hospital cares for all illnesses of children excepting pulmonary tuberculosis and contagious diseases The hospital is governed by a permanent Board of Trustees It

is supported by the income from its endowment fund, contributions from patients, receipts from the care of city, county and state patients, and by funds allotted by the Detroit Community Fund



FIG 6 Children's Hospital of Michigan

In 1934, 6,449 patients were admitted to the hospital and 73,822 days' care were given, 7 800 new patients were cared for in the out-patient department and 84,000 patients' visits were made there, 550 patients were admitted to the Convalescent Home and were given 65,846 days' care

The hospital maintains a school for teaching pediatric nursing to senior students from accredited training schools and to postgraduate students

THE WAYNE COUNTY MEDICAL SOCIETY

The Wayne County Medical Society was organized as a branch of the Michigan State Medical Society in 1849. The law under which it operated was repealed in 1851. The Detroit Medical Society functioned as its successor until 1866, when it was reorganized under its old name. In 1876 the Society was incorporated and had an active period of several years. Professional interest became divided by the organization of the Detroit Academy of Medicine by the faculty of the Detroit Medical College and the Detroit Medical and Library Association.

The Wayne County Society was kept alive by a small socially congenial group.

The Medical and Library Association, at that time the dominant society of the city, was compelled, by the adoption of the present membership requirements of the American Medical Association, to disband and transfer its membership to the Wayne County Society, which then became the powerful organization that it is today. In 1909 it purchased a property and added to

it a library building and an auditorium. Later the library was put in charge of the public library of the city, and with the organization of Wayne University it was transferred to the medical department and is now housed in the college building. In 1932 the Society removed to its present building acquired through the generosity of a public minded citizen. It is now the center of medical activity in the city. It has a membership of over 1,500, the fourth largest county medical society in the country. Its club features



FIG 7 The Wayne County Medical Society Building

make it a popular daily meeting place for medical men. Through its various committees it takes a prominent part in civic affairs of medical interest, especially in the fields of social service, the medical care of the indigent and the safeguarding of the proper interests of the medical profession.

THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR *

The University was founded in 1817 when the Governor and the Judges of the Territory of Michigan, which then had a population of less than

* Contributed by Frederick G. Novy, M.D., Sc.D., LL.D., Dean Emeritus of the Medical School

7,000, passed an Act establishing the Catholepistemiad or University of Michigan. This Act provided for thirteen professorships, designated as didaxia, one of which was specified as iatrica or medical sciences. The sponsors of the Act were John Monteith, a Presbyterian minister, Gabriel Richard, a French priest, and A. B. Woodward, a Judge. The germ of the idea of a medical school thus was incorporated in the proposed structure, possibly the sponsors had in mind the case of Nathan Smith who first at Dartmouth and later at Yale constituted the whole medical faculty.

A new Act was passed in 1821, repealing the former one, and creating a University of Michigan at Detroit. The Trustees of the new University did little more than to secure from Congress the grant of valuable lands for its support, some of which they promptly sold at a very low figure.

On January 26, 1837, Michigan, then having a population of about 100,000, was formally admitted as a State into the Union. Shortly before this date, the Superintendent of Public Instruction, the Reverend J. D. Pierce, a graduate of Brown, presented a comprehensive educational plan, based on the Prussian system. As a result, the Legislature of the new state, on March 18, passed the Organic Act establishing the University of Michigan, and two days later another Act was passed locating the University at Ann Arbor. In the first Act it was specified that the University was to consist of three departments. The Department of Literature, Science and Arts, the Department of Law, and, the Department of Medicine. The first of these departments was opened in September 1841.

The Department of Law, perhaps, should have been the next to be established, but in January 1847, a petition was presented to the Board of Regents asking for the organization of the Medical Department. Owing to an adverse legal opinion no action was taken at the time. However, a year later, the Board formally adopted a report whereby the School was established, money was appropriated for a laboratory building, and professors were appointed. After some delay, due to lack of funds, the Medical Building was finally completed and when its doors were opened to students in the fall of 1850, a faculty of five professors were on hand to give instructions.

The Medical Department was the first professional school established at the University. This example of Michigan in providing for medical education at a university was taken up, largely by the newly formed western states. At the present time 30 state universities have medical schools. Moreover, the new Medical School was an integral part of the University and not a merely nominal connection as was often the case. The professors were salaried and the equipment was provided by the University.

Because of its financial independence, the new medical school was able to carry out policies which otherwise might have been very difficult. Thus, it started out with a course of two years of six months each. In those days the course of instruction in the medical colleges of the country, almost without exception, extended only over four months. The apprenticeship system was



FIG 8 University of Michigan Hospital

in vogue and since the instruction was given largely by lectures and recitations it was required for graduation that the student exhibit evidence of having pursued the study of medicine and surgery for the term of three years with some respectable practitioner of medicine (including lecture terms) This preceptorial system lasted for three decades



FIG 9 University of Michigan Medical School, West Medical Building

In 1878, the course was lengthened to two years of nine months each, and in 1880 to three years of nine months each. This increase in time was brought about by the introduction of laboratory courses and hospital instruction. In 1890, the course was extended to four years of nine months each, thus permitting the further development of a graded course for the teaching of the rapidly growing basic sciences and the expanding clinical work. Another step taken at this time was the establishment of the first Combined Course in Arts and Medicine. This combination, though criticized at the time, has since been generally adopted by other universities.

The entrance requirements for the Medical School in 1850 were much the same as those for entrance to the Literary College but gradually they were modified so that only "the elementary branches of an English education" remained.

With the increase in the length of the course and the teaching of the new sciences it became evident that the requirements for admission should be raised. Hence, it was that in 1890 they were advanced to a diploma from

the classical course in an approved high school, and a little later, in 1896, the requirement of certain languages and science subjects was made effective

In 1909, the minimum requirement for admission was placed at two years of collegiate work, and in 1929, this was increased to 70 hours, and, in 1931, it was advanced to 90 semester hours

The School which opened in 1850 with five professors now maintains a staff of 24 professors, 19 associate professors, 23 assistant professors, 78 instructors and 82 assistants, or a total of 226. The dean is A. C. Furstenberg.

Laboratories were not a conspicuous part of the medical schools of 1850. True, rooms for dissection were provided but the other sciences were either in their infancy or as yet unborn. The chair of Anatomy at the University was first filled by Moses Gunn who later became professor of surgery and eventually was called to Rush Medical College. He was followed by Corydon L. Ford who held the position for 40 years. Then came J. P. McMurrich who after 12 years of service accepted the chair at Toronto, his successor was G. L. Streeter who after a few years left to take charge of the newly organized Carnegie Institution in Baltimore. The department was then combined with histology under G. C. Huber and R. E. McCotter.

Histology as an offshoot of anatomy was recognized in 1877 as a separate study when a laboratory was equipped, and in 1879 by the appointment of C. H. Stowell, but in 1889 it was temporarily combined with physiology under W. H. Howell. After a short time the work was taken over by G. C. Huber who carried on until his death in 1934.

At Michigan, some laboratory chemistry was at first given in the old Medical Building and with such success that it led, in 1856, to the construction of the first chemical laboratory in a state university, if not the first in the country. The original small building was repeatedly enlarged and finally in 1909 the present laboratory was completed and occupied. It was in the old chemical laboratory that physiological chemistry developed in the seventies. The first chairs in this subject were filled at Yale by Chittenden and at Michigan by V. C. Vaughan at about the same time. After a few years the chair was combined with hygiene, and Vaughan held the dual position until his retirement in 1921. His successor in physiological chemistry is H. B. Lewis.

Physiology was first an appanage of anatomy under C. L. Ford and a laboratory was established in 1877, but the modern experimental phase began with Henry Sewall who entered on his work as professor in 1881. Because of ill health he was forced to retire and was succeeded in 1889 by W. H. Howell who held the position until 1892 when he went to Harvard and a year later to Johns Hopkins. He was followed by W. P. Lombard who retired in 1923 to be succeeded by R. Gesell.

Pathology was likewise in the early days combined with another chair,

namely medicine, under A. B. Palmer. After his death in 1887, an independent chair was created under H. Gibbs, and laboratory work was instituted. In 1895, the chair was recombined with medicine under George Dock, the actual instruction being carried on by A. S. Waitlin who filled the chair until his death in 1931. His successor is C. V. Weller.

Materia medica and therapeutics were at first tied up with chemistry, later passed on to anatomy, physiology, ophthalmology and, again, with medical chemistry, or given independence for a short time. In 1890, however, the chair of Pharmacology was established under J. J. Abel who, in 1893, left to join the Johns Hopkins faculty. He was followed by A. R. Cushny who, in 1905, was called to London and later to Edinburgh. His successor is C. W. Edmunds.

In 1888, the Hygienic Laboratory was built from a special appropriation of the Legislature, and the first systematic instruction in bacteriology given in this country was begun under F. G. Novy who retired in 1935 and was succeeded by M. H. Soule.

It will be seen from the above that the importance of the sciences was early recognized and every opportunity was given for their development. Today the School is provided with three large and commodious buildings for instruction and research in the basic sciences.

Of clinical instruction in the present sense, there was but little during the first two decades. At first, some effort was made to give such instruction in a summer session in Detroit but this was attended with little success. The location of the medical school in a small city, such as Ann Arbor at that time, was decidedly unfavorable from a clinical standpoint and repeated attempts were made to have the school removed to Detroit but with no success. In the absence of hospital facilities the clinical staff invited physicians to bring in their patients on three mornings in the week for diagnosis and demonstration. This custom had a beneficial result for before long patients did present themselves at these modest clinics. They were then brought into the lecture room of the old Medical Building where they were examined before the class and, if need be, operated upon and then carried to a private house for subsequent care.

In 1869, the beginning of a hospital was made when one of the four professors' houses on the campus was fitted out for that purpose. This did not relieve the situation materially and, in 1875, the Legislature was prevailed upon to appropriate a small sum of money for a wooden pavilion hospital, of the type used during the Civil War, which was to be connected with the former building. It was argued that a hospital would become so infected in time that it would be necessary to burn or demolish it and replace it with a new one. However, the new pavilion hospital proved its need and the Legislature of 1879, 1881, and 1883 was prevailed upon to make further appropriations, at no time exceeding \$7,000, for additions such as a women's ward, a ward for eye and ear cases, and a clinical amphitheater.

By 1889 the wooden hospital on the campus had more than reached its

limit and again the legislature was called upon to relieve an intolerable situation. This time it appropriated what seemed to be a very large sum (\$100,000) for the erection of a new brick hospital on the hill overlooking the Huron River. In the following years repeated additions and extensions were made, but the conditions became far from satisfactory because of the increasing demand for medical and surgical service on the part of the citizens of the state. Serious thought was given to the building of a new and thoroughly modern hospital. The Legislature was again appealed to and this time a grant of one million dollars was made. Before construction was entered on we were involved in the World War and the matter was postponed. After the War it was clear that the amount appropriated would be insufficient and further requests were presented to the Legislature with the result that enough funds were provided to erect the present new hospital which was opened in 1925. It has a capacity of 835 beds and since some of the old buildings have been retained the entire hospital has a capacity of 1,312 beds. It is essentially a teaching hospital and as such is unique. The most recent addition is a therapeutic pool primarily intended for cases of poliomyelitis.

A state psychopathic hospital was erected on the hospital grounds in 1906. It was the first University building for psychiatric teaching to be established in this country. It has a capacity of 62 beds and in the near future it will be enlarged to provide 90 beds.

Adjoining the main hospital is the Simpson Memorial Institute for Medical Research, opened in 1927, and primarily devoted to the study of pernicious anemia and other blood diseases.

As might be expected, of the five original appointments to the faculty, three were clinical, namely, surgery, medicine and obstetrics, including diseases of women and children. The specialties were to come later.

In surgery, in the interval of 63 years between Gunn and the present incumbent, F. A. Coller, there were six professors. The surgery staff at present numbers 37 of whom 10 hold the rank of professor. With two exceptions all are on full time. Besides general surgery, there are subdivisions of neuro-surgery, orthopedics, thoracic surgery and urology.

The head of the Department of Medicine is C. C. Sturgis who is also the eighth appointee to the chair. The staff consists of 27 full-time men, of whom 9 rank as professors.

The Department of Obstetrics and Gynecology is in charge of N. F. Miller who is the fifth to hold that chair.

Ophthalmology and aural surgery was one of the first specialties to be recognized (1872). It was divided in 1904 and the present head of the former is F. B. Fralick while the Department of Otolaryngology is headed by A. C. Furstenberg.

Neurology was recognized as an entity in 1888. This work is in charge of C. D. Camp.

Dermatology was introduced into the curriculum in 1890 and is headed by U J Wile

The Department of Pediatrics was dissociated from Obstetrics in 1901 and ever since has been conducted by D M Cowie

The chair of Psychiatry was established in 1906 and given to A M Barrett who is the present head of the Department

Roentgenology was the last of the special chairs to be created and the work is now in charge of F J Hodges

A Department of Postgraduate Medicine is maintained for the purpose of giving instruction to practitioners. Special courses are given in different parts of the state. This work is in charge of J D Bruce

ANNALS OF INTERNAL MEDICINE

VOLUME 9

FEBRUARY, 1936

NUMBER 8

GROWTH AND DEVELOPMENT OF FUNCTION IN BLOOD VESSELS AND LYMPHATICS

By ELIOT R. CLARK, M.D., *Philadelphia, Pennsylvania*

PROBLEMS relating to the growth and development of function in blood vessels and lymphatics are not restricted to the period of embryonic development and the growth period, but are met with throughout the entire life of the individual. They play a particularly important role in the reparative stages of inflammation, in the reaction to various forms of injury, and in the healing which follows surgical operations. The development in our laboratory of a special technic enables us to make observations of many continuous hours daily, extending over weeks and months, with the highest powers of the microscope, in which we can observe directly the minutest morphological details of the growth of blood capillaries, the differentiation of arteries and venules and their behavior in relation to function, and the growth and behavior of lymphatic vessels.

The method, first worked out with the assistance of Mr. Sandison and perfected and extended by a group including Drs. R. G. Williams, H. T. Kirby-Smith, R. O. Rex, R. G. Abell, W. J. Hitschler, Mrs. Clark and myself, consists of the permanent installation in the ear of a rabbit or other mammal of a double-walled transparent chamber, in which there is left a central round "table" space, in relation with the living tissue of the ear. This space fills with exudate, blood cells and fibrin, which in turn is invaded by new tissues—including blood-vessels, lymphatics, connective tissue, and nerves—from the surrounding living tissues. The thickness of the space varies in different chambers from 45 to 75 micra. Modified types of chamber are also in use which permit the study of the original tissues of the ear, the introduction of chemical substances (Abell and Clark), and the access to the living tissue for experiment, transplantation or manipulation (R. G. Williams). No anesthesia is required during the observation period.

First the rate of growth of new blood capillaries will be considered. They appear at the edge of the "table" at an average of seven days after the installation of the chamber and advance at a rate which varies from 0.2

* Received for publication April 29, 1935.
From the University of Pennsylvania, Philadelphia, Pa.

to 0.6 mm a day, under favorable growth conditions. There is evidence that the rate of advance may be influenced by temperature, at least to the extent that marked lowering of the room temperature may result in slower growth. There is also evidence that the rate of advance is affected by the condition of the substances into which the capillaries are growing. Thus in chambers with a minimum of disturbance, in places where no hemorrhages or inflammatory exudations have occurred for several days, the rate of growth is appreciably reduced. However, there is much still to be learned regarding the physical and chemical factors which regulate the growth of new capillaries, and studies in this direction are going on in our laboratory.

Regarding the manner of growth of new blood capillaries, it has been possible to establish definitely that they grow by the sending out of sprouts from preexisting capillaries, in a manner similar to that established years ago in the transparent tails of amphibian larvae. Pointed endothelial processes are pushed out from the side of a circulating capillary or venule into the base of which the lumen gradually extends, and into which the nuclei are carried by the amoeboid activity of their surrounding endoplasm. The tip is constantly extended until it comes in contact with a blood capillary, venule or another sprout, when it forms a connection through which the lumen gradually extends. The nuclei increase in number by mitotic division—a process which has been observed in the living rabbit. No outside cell contributes to this endothelial extension. In fact, such sprouts have been seen to grow through a fibrin network—which no fibroblasts had yet penetrated and in which leukocytes could be easily excluded as possible contributors. The number of new sprouts for a given area varies enormously—from an occasional single sprout to a density so great that the neighboring sprouts are almost in contact with one another. Many sprouts may grow out from the wall of a single capillary or venule. Since this property of growth is probably common to endothelium of all capillaries and veins, it may be stated that, if suitable growth conditions are introduced, the number of capillaries of any region of the body may be increased many-fold within a period of two or three days.

However, growth processes also operate in the reverse direction, and many of the newly formed capillaries retract or disappear, in some instances by a process which is the reverse of sprouting, in others by what appears to be a dissolution of the endothelium. Thus, in places not more than one out of 10 of the newly formed capillaries survives, while in others nearly all may survive. Loss of capillaries is greater in the neighborhood of arterioles than in that of venules. This process of reverse growth, while varying in rate, may occur so rapidly that short capillaries may narrow and retract within 24 hours.

Nearly as rapid as the growth of new capillaries is the development of arteries and veins, both of which are formed by the enlargement of capillaries or parts of capillaries. Within a few days a newly formed capillary

may enlarge to form part of an arteriole or venule. The determining factors as to which of four fates may befall a capillary (retention as a capillary, disappearance, or enlargement to form part of an artery or vein) lie chiefly in the two hydrodynamical forces, blood pressure and amount of blood flow, as pointed out by Thoma in his histomechanical principles, the former regulating the thickness of the wall and the latter the size of the lumen.

While the endothelium is the essential tissue of the vascular system, forming a complete lining probably for all parts of it, leading the way in all its growth extensions and constituting a membrane through which occurs all interchange between the blood stream and outside cells and spaces, there is an elaborate development of accessory or adventitial cells outside, which ranges from the smooth muscle, connective tissue, elastic tissue wall of the larger arteries to scattered adventitial cells on capillaries and venules. These layers act as mechanical supports to the system and also, in connection with the nervous system, as local regulators of the flow of blood. Regarding these tissues outside the endothelium we have been able to make certain interesting observations.

The first adventitial cells on blood capillaries appear very early in their formation, often on new sprouts which have not yet connected with other capillaries and practically in all cases soon after circulation starts in the new capillary. In the tadpole's tail their formation from the surrounding connective tissue cells has been established by Mrs. Clark and myself, and we have observed in the mammal the flattening on the newly forming capillary of cells from outside—from the army of fibroblasts which usually invades the space along with the blood capillaries. Persistent study of some 40 such cells carried out during the past three weeks on a set of about a dozen capillaries indicates that the original early quota may remain unchanged for weeks, although one cell was seen to undergo division into two. In the capillaries in the rabbit's ear they are as inert as we had found them in the tail of the tadpole, and we cannot agree with Krogh, who has rather unfortunately termed them "Rouget" cells, that they play any part in capillary contraction.

On the arterioles there is a rapid increase in the number of cells outside the endothelium, the exact origin and development of which have not yet been worked out. However, the tempo and certain other details of development are of interest. Within two or three days one sees on the arterioles, in place of the longitudinally arranged cells, a continuous layer of cells which encircle the arteriole. Coincident with or following soon after this the arteriole becomes narrower. Just how soon this cell may be called a muscle cell we do not know. It apparently does not perform definite contractions and dilatations unless and until a vasomotor nerve reaches it. Regarding the latter, Dr. R. G. Williams, Mrs. Clark and I have been able to link up the inauguration and extension of definite contractions and dilatations with the ingrowth of nerves, by the use of intravital methylene blue

staining, and have proved the presence of active muscle cells which performed nerve controlled contractions on a vessel which 10 days before had been a newly formed capillary sprout. We also observed the extension of this undoubted contractility to muscle cells on parts of the vessel which ranged between 10 and 18 days of age. We have evidence of definite muscle contractility on arterioles 8 and 9 days old, respectively, which must for the present stand as the minimum time in which a new smooth muscle cell may develop. While muscle cells develop on all arterioles and apparently maintain a persistent partial contraction, only a variable fraction of the new arterioles in a regenerated region are reached by vasomotor nerves, and it is only the latter which develop typical contractions and dilations. Thus we have some chambers in which not a single arteriole showed this activity even after months. However, we have seen active contractility develop as late as $7\frac{1}{2}$ months after the growth of the arteriole.

While capillaries ordinarily intervene between artery and vein, it has long been known that in the ears of rabbits, as in certain regions of other animals, there are direct connections, or arterio-venous anastomoses. It has been possible in our chambers to observe the behavior of such structures, to watch their development and to discover some of the factors which regulate their formation and persistence. They are regulated in part, at least, by circulatory conditions.

In speaking of the development of the arteriole we have referred also to its function. Let us return briefly to consider the development of function in the capillary. We may exclude the development of contractility in the capillary, since the most prolonged observation and rigid testing, first by Sandison and later by Miss Clark and myself, have convinced us that neither in the ear of the rabbit nor in that of the dog does endothelium possess any such power of contractility as is usually associated with control of blood flow. This is of extreme interest and importance, of interest because the endothelium of capillaries in the tail of amphibian larvae has undoubted active contractility (and suggests an evolutionary loss of this property following the elaborate development of the nerve-muscle apparatus on the arteries in mammals), and of importance because it directs the physiologist back to smooth muscle and nerve in analyzing the control of peripheral circulation, perhaps saving him from a wild-goose chase in an attempt to discover the details of an endothelial contractility which probably does not exist in the mammal.

Regarding the essential function of the capillary, however, that of furnishing a membrane through which interchange of substances takes place, it is interesting that this function apparently starts as soon as circulation begins in a new capillary—perhaps earlier. However, the newly formed capillary differs slightly from the older capillary in its consistency, for it is obviously softer and more tender. Thus newly formed capillaries frequently become widened to a diameter three or four times the usual capillary size and are so tender that small hemorrhages from them are easily produced.

by slight external pressure or even by increased blood pressure. This soft consistency changes rapidly, especially in those capillaries with abundant blood flow, and within a day or two the new capillary grows narrower and is more resistant to injury.

The soft consistency of the young capillary is a property which may be manifested by well-established capillaries under the influence of chemical substances. There is evidence that blood-vessel endothelium may at any time, in reaction to certain chemical or mechanical stimuli, undergo progressive changes in consistency which are evidenced by (1) mild sticking of leukocytes to the endothelium, (2) prolonged leukocyte sticking, (3) emigration of leukocytes, (4) localized bulgings and hemorrhages, and (5) disintegration of endothelium. Such changes are most conspicuous in but not confined to inflammation.

The growth of lymphatics as observed in the rabbit's ear shows both similarities and differences when compared with blood vessels. Like blood vessels, growth takes place by the sending out of endothelial sprouts, into the bases of which the lumen gradually extends. All new lymphatic endothelium forms from preexisting lymphatic endothelium, and nuclei increase in number by mitotic division. The lymphatic is *normally* closed, both during growth and subsequently.

On the other hand, the growth of lymphatics is much more sporadic than that of blood vessels. Thus in the many chambers which have been observed, there have been great variations in the time and extent of ingrowth of lymphatics. In some cases one or more lymphatics have grown along with the most advanced blood capillaries, in others the first lymphatics have not appeared on the table until a week or more after the space has been completely vascularized. When lymphatics advance after blood vessels and connective tissue have differentiated, they show a decided tendency to grow along a clear space next an artery or a vein. They may continue a slow growth for weeks. Because of the almost negligible pressure in lymphatic capillaries they may be compressed along their course, and terminal stretches may be left completely isolated. Such isolated lymphatics may persist for weeks, retaining their typical lymphatic endothelial properties. They may eventually reunite with other lymphatics or may gradually shorten and disintegrate.

While lymphatics are normally closed, their contents may be forced through the wall by light pressure. If surrounded by the normal semigelatinous intervascular material, openings so made close at once. If, however, there is free fluid surrounding them, we have observed such artificial openings to persist for days, with an in-and-out movement of fluid and floating cells.

The frequent close proximity of venule and lymphatic makes possible a break of the double endothelial wall, with hemorrhage into the lymphatic. Such openings have, in our observations, always closed immediately, leaving a mass of blood in the lymphatic. While such a mass of erythrocytes in

the lymphatic may be cleared out within 24 hours, some of the erythrocytes may, in the absence of massage, remain in the bulbous tips for many days

As for the development of function in the lymphatic, we have been impressed with the very slight amount of activity manifested by the lymphatic capillaries as watched in the living, under the conditions of our observations. There is some passage of fluid into the new vessels, but it is apparently slight in amount. Thus floating cells in the lymph may be seen bobbing back and forth for minutes or even hours without progressing. We have frequently seen not only erythrocytes but immigrated leukocytes remain in a lymphatic tip for weeks. The lymphatics play no significant part in the removal of the enormous amount of extravasated erythrocytes and other debris which is present following the insertion of the chamber or after a hemorrhage, and which is removed without their assistance. In inflammatory conditions with edema the lymphatics become distended but usually show even a diminution in flow indicating a blocking. There is no noticeable difference in the rate or amount of connective tissue growth in our chambers, whether lymphatics are present or absent. Regions without lymphatics show no evidence of disturbed physiology. In short, our own observations on the behavior of living lymphatics corroborate other studies on the sluggishness of lymph flow from peripheral parts of the body in mammals, in the absence of muscular activity. They even raise the question as to whether, in such regions, lymphatics play any useful role whatever.

The observations which have been presented in this paper regarding the growth and behavior of blood vessels and lymphatics as seen through the microscope in the living mammal represent but samples of the studies which a new method has made possible. They form a mere beginning of a new analysis of that region which is of such fundamental importance in the anatomy and physiology of health and disease, namely, the peripheral region which includes the arteriole and venule, the blood and lymphatic capillary, the cells of the tissues, and, scarcely less important, the extravascular, extra-cellular tissue spaces.

The paper was illustrated by lantern slides and by an eight minute motion picture film made with the assistance of Dr. E. A. Swenson, which showed the circulation in new-growing and recently formed blood vessels, movement of blood cells in an isolated lymphatic, and contraction and dilatations of a new-formed arteriole and of a new-formed arterio-venous anastomosis.

REFERENCES

- SANDISON, J. C. The transparent chamber of the rabbit's ear, etc, *Am. Jr. Anat.*, 1928, *vi*, 447-473.
- CLARK, E. R., KIRBY-SMITH, H. T., REA, R. O., and WILLIAMS, R. G. Recent modifications in the method of studying living cells and tissues in transparent chambers inserted in the rabbit's ear, *Anat. Rec.*, 1930, *xlvii*, 187-211.
- CLARK, E. R., HITSCHLER, W. J., KIRBY-SMITH, H. T., REA, R. O., and SMITH, J. H. General observations on the ingrowth of new blood vessels into standardized chambers in the rabbit's ear, etc, *Anat. Rec.*, 1931, *i*, 129-167.
- CLARK, E. R., CLARK, E. L., and WILLIAMS, R. G. Microscopic observations in the living

- rabbit of the new growth of nerves and the establishment of nerve-controlled contractions of newly formed arterioles. *Am. Jr. Anat.*, 1934, *lx*, 47-77
- CLARK, E. R., and CLARK, F. L. Observations on living arteriovenous anastomoses as seen in transparent chambers introduced into the rabbit's ear, *Am. Jr. Anat.*, 1934, *lx*, 229-285
- CLARK, E. R., and CLARK, F. L. The new formation of arteriovenous anastomoses in the rabbit's ear. *Am. Jr. Anat.* 1934 *lx* 407-467
- SANDISON, J. C. Contraction of blood vessels and observations on the circulation in the transparent chamber in the rabbit's ear. *Anat. Rec.*, 1932 *liv*, 105-127
- CLARK, E. R., and CLARK, F. L. Observations on changes in blood vascular endothelium in the living animal. *Am. Jr. Anat.* 1932 *lxii* 385-437
- CLARK, E. R. and CLARK, F. L. Observations on the new growth of lymphatic vessels as seen in transparent chambers introduced into the rabbit's ear. *Am. Jr. Anat.*, 1932, *li*, 49-87
- CLARK, E. R. and CLARK, E. L. Further observations on living lymphatics in the transparent chambers in the rabbit's ear—their relation to the tissue spaces. *Am. Jr. Anat.*, 1933 *liii*, 273-305

THE PRESENT STATUS OF BRONCHOSCOPY IN BRONCHIAL ASTHMA^{*}

By LOUIS H. CLERG, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

IN a discussion of bronchial asthma one should bear in mind that patients sent as cases of asthma for investigation or treatment often present signs or symptoms that do not conform to the textbook description of this condition. In other words, there are many pathologic conditions that simulate asthma and may be regarded clinically as such. It is only by a careful study that the correct diagnosis is made. The rôle of bronchoscopy in bronchial asthma therefore includes the investigation of the tracheobronchial tree to rule out certain conditions that might simulate asthma. In addition bronchoscopy permits the collection of bronchial secretions for autogenous vaccine, and it affords relief by removal of obstructing secretions from the air passages. The interest of the bronchoscopist is limited largely to that form of asthma associated with evidences of tracheobronchitis, the so-called bacterial asthma. Hypersensitiveness and the part played by bacteria as an etiological factor in asthma are problems for the allergist.

The matter of diagnosis is often difficult. Not infrequently patients with dyspnea, wheeze or cough of obscure origin are referred to the bronchoscopist for investigation and it is found these are clinical manifestations of hypersensitiveness. On the other hand patients with a foreign body in the air passages or even in the esophagus not infrequently have been studied carefully from an allergic standpoint, and only later has it been discovered that there was a good foreign body history with quite typical signs and symptoms.

One of the common and often most misleading symptoms which suggest a provisional diagnosis of asthma is wheezing respiration. It is usually described as "asthmatic wheeze," a term which promptly offers a diagnostic possibility to those who are readily influenced by suggestion. The wheeze, heard best at the open mouth and towards the end of expiration, should be considered as an audible manifestation of *narrowing of the airway*. Mechanical conditions producing the wheezing sound are perfectly obvious to the bronchoscopist, namely, air being forced through a narrowed lumen. In the patient with foreign body the narrowing is produced by the foreign body, swollen inflammatory mucosa and secretions, in the asthmatic patient air is being forced through a lumen narrowed by congestive or inflammatory changes, and with thick mucoid secretion adherent to its walls. It has been described also as a symptom of laryngeal disease, of foreign body in the trachea or bronchi, of foreign body in the esophagus, of malignant or benign tumor of the trachea or bronchi, of compression stenosis or of stricture of a bronchus. Why not describe it as "wheeze" or "wheezing

^{*} Received for publication November 25, 1935

respiration" without reference to asthma and then proceed to investigate it as a symptom indicative of partial obstruction to the airway? It is in this connection that bronchoscopy and at times esophagoscopy have given valuable aid in establishing a correct diagnosis and often effecting a cure. Illustrative cases are cited.

Case 1 A woman, aged 31 years, reported to an Allergy Clinic for investigation of wheezing respiration and a slight cough of three weeks' duration. Routine skin tests were carried out and the patient was requested to bring in a quantity of house dust. Following the third visit she was advised that all of the tests were negative and that she did not have asthma. Curiously, the wheeze disappeared at about that time being replaced by slight dyspnea and an aching sensation in the left chest. She consulted another physician who examined her chest and referred her to the Bronchoscopic Clinic of Jefferson Hospital for investigation of atelectasis of the left lung. Completed studies revealed a malignant tumor of the left bronchus.

Comment The symptom "wheezing respiration" led the patient to believe that she had asthma. This provisional diagnosis apparently was accepted at the Allergy Clinic, for no chest studies were carried out. When the bronchial obstruction became complete, producing atelectasis, the wheeze disappeared.

Case 2 A child, aged two years, began to wheeze during August. This was noted particularly during sleep. There was also some dysphagia for solid food. Later, slight dyspnea developed. After several months it was observed that paroxysms of dyspnea with wheezing occurred whenever the child took any food. A diagnosis of asthma was made and several foods were suspected. Avoidance of these gave no relief. The symptoms became progressively worse, epinephrine afforded some comfort. On careful questioning it was found that the child had swallowed a large button about three weeks before the onset of symptoms. Roentgen studies of the swallowing function revealed a non-opaque object in the cervical esophagus. At esophagoscopy this proved to be a button. Its removal seven months after it had been swallowed was followed by prompt relief of the asthmatic symptoms.

Comment The large size of the foreign body together with the periesophageal swelling produced compression stenosis of the trachea which was responsible for the wheeze and later the dyspnea. The dysphagia apparently was overlooked.

Foreign body as a diagnostic possibility should be excluded in every child presenting symptoms suggesting asthma. A careful study of the history and symptoms, a thorough physical examination of the chest supplemented by a roentgen study will rule out foreign body in a majority of cases. If in doubt a diagnostic bronchoscopy is indicated. Wheezing respiration is a common symptom of bronchial foreign body.

Bronchoscopic observations in the cases of true asthma are of interest. The noteworthy findings are collapse of the trachea and bronchi during cough and forced expiration, and the presence of abnormal secretions.

Collapse of the Trachea and Bronchi Moderate forward bulging of the membranous wall of the trachea during cough is often observed in children, occasionally in adults, and is not considered pathologic. In the normal person there is a rhythmic movement of the trachea and bronchi during respiration. The bronchi elongate and dilate during inspiration, during expiration they shorten and contract. These changes are participated in by the entire bronchial tree. The collapse observed in certain cases of asthma differs from the normal phenomenon both in appearance and in the mechanism involved in its production. At the beginning of expiration in many cases there is noted marked collapse of the trachea. In some the collapse is limited to the posterior tracheal wall, which, bulging forward, becomes convex, and fits into the concavity of the anterior wall of the trachea, the resulting lumen is crescentic. The forward bulging occurs during expiration and cough, and is in proportion to the force of the expiratory effort. Occasionally the lateral tracheal walls also participate in the collapse, giving the lumen a triangular appearance. The lumen promptly returns to its normal more or less rounded appearance at the beginning of inspiration. In many of these cases there is an associated collapse of the walls of the bronchi including the orifices of the bronchial subdivisions. These changes often are sufficiently marked to interfere with the introduction of the bronchoscope which can be advanced only during inspiration. This is not bronchial spasm. The collapse is undoubtedly passive in nature, and one gains the impression that the tracheal and bronchial walls are being forced shut by some external influence. This phenomenon was discussed by F. J. Kaltefleiter in a previous report. While not absolutely characteristic of the average case of asthma, it is unquestionably a pathologic state that is present in certain of the different conditions clinically described as asthma.

Treatment In my experience bronchoscopy has been employed only in cases that did not present any demonstrable etiological basis for their symptoms or did not respond to treatment based on supposed causative factors. With an occasional exception our patients had been studied from the standpoint of allergy, and the nasal accessory sinuses, the teeth and other possible foci of infection had been investigated. Their status as to the presence or absence of serious organic disease had been determined.

These patients could be divided roughly into two groups. The first consisted of adult patients who, previously well, dated the onset of asthmatic symptoms to an acute respiratory infection. The second group consisted largely of children. In these the asthmatic symptoms were sudden in onset and often were considered as of foreign body origin.

In the first group the more commonly observed symptoms were a sense of tightness or constriction about the chest and cough. Paroxysmal attacks of coughing often initiated the asthmatic attacks. Mucoid or thick mucopurulent sputum was present. When sputum was readily coughed up the patient seemed comfortable. From a description of the paroxysms of asthma one gained the impression that the inability of the patient to get rid

of secretions was followed by subjective sensations in the chest, paroxysms of cough with dyspnea and wheezing. The hypodermatic use of epinephrine often gave little relief, occasionally it produced a feeling of depression with severe headache. Atropine and morphine often were helpful. Burning of "asthma powders" seemed to give greater temporary relief than any of the commonly employed measures. Attacks would continue for hours, even days. Relief was secured following expectoration of secretions. The patients commonly exhibited the clinical and roentgen findings observed in chronic laryngotracheobronchitis. Suppuration of the nasal accessory sinuses often was present but no relief was secured from treatment. A history of many nasal operations was the rule. It was not uncommon to find allergic reactions to certain substances including house dust. Attempts at desensitization either failed to give relief or produced only slight amelioration of the attacks.

The bronchoscopic findings consisted of moderate inflammatory changes involving the mucosa of the larynx, trachea and larger bronchi with thick mucoid or mucopurulent secretion adherent in small clumps to the walls. One always could secure an additional quantity of this by exploring the smaller bronchial subdivisions with a small flexible tipped aspirating tube. Narrowing of the orifices of the smaller bronchial subdivisions was no greater than would be expected in the presence of chronic inflammatory swelling of the mucous membrane. Collapse of the trachea and larger bronchi during expiration occurred. Patients observed during a paroxysm did not yield any additional information unless dyspnea was marked. Then the expiratory collapse of the airway was increased and the mucosa appeared more cyanotic.

The following fairly typical case is cited

Case 3 A female, aged 25 years, had asthmatic attacks for six years. There was a history of an acute pulmonary infection about two years previously, but recovery was apparently complete. Shortly before the onset of the asthmatic attacks the patient had a severe "head cold" which continued for about two months. During the past six years she had been under the care of many physicians, 10 operations on the nasal accessory sinuses had been performed, and in addition the tonsils had been removed. A number of skin tests were carried out with negative results and vaccine therapy was employed with little benefit. During the year prior to admission to the Bronchoscopic Clinic, Jefferson Hospital, she had secured little relief from attacks. On admission she had not been free from wheezing and dyspnea for practically three months. The usual forms of medication gave slight relief. A roentgen study of the chest revealed little change. Although the patient's condition was not good bronchoscopy was proceeded with. A large quantity of thick tenacious mucopus was found in the trachea, main bronchi and their subdivisions. There was a generalized tracheobronchitis. Collapse of the trachea and large bronchi was noted during expiration and cough. The patient developed a severe paroxysm of asthma during the bronchoscopy, with removal of a large quantity of secretions there was marked alleviation of symptoms. Vaccine made from the bronchoscopically removed secretions was given with no apparent benefit. Repeated bronchoscopic treatments have been carried out in this patient, in fact, she has been reporting to the Bronchoscopic Clinic

every three or four weeks for the past four years. She is willing to continue since this is the only mode of treatment that has afforded relief.

The second group of cases was characterized by the abrupt onset of the asthmatic symptoms, often suggesting foreign body aspiration. All of the patients observed were children. In one case the attacks occurred only during rainy weather. In others no predisposing factors could be elicited. The acute onset with wheezing respiration, alarming dyspnea both expiratory and inspiratory, a moderate febrile reaction and clinical and roentgen findings of bilateral obstructive emphysema warranted bronchoscopic investigation to rule out tracheal or bilateral bronchial obstruction, notably foreign body. Through the bronchoscope there was found a subacute tracheobronchitis with a large quantity of tenacious, greyish secretion in the trachea and bronchi. The relief secured following bronchoscopic aspiration of the secretions was not unlike that observed after removal of a partially obstructing tracheal foreign body. In the subsequent studies of these cases nasal accessory sinus disease and positive skin reactions, particularly to foods, often were found present. I do not recall a single case in this group, however, that was benefited by removal of suspected foods or by attempts at desensitization.

The following case is typical.

Case 4. A child, aged two years and nine months, daughter of a physician, was brought to the Bronchoscopic Clinic with wheezing respiration and severe dyspnea. There was moderate fever. The onset had occurred quite abruptly 24 hours previously. A provisional diagnosis of asthma had been made, and epinephrine, atropine and morphine had been given without relief. Foreign body was then suspected although there was no history of foreign body aspiration. On admission the dyspnea and wheezing were both expiratory and inspiratory. There was no cyanosis. Cough was absent. The findings suggested tracheal obstruction. Roentgen study by Dr. W. F. Manges showed overdistention of both lungs with air throughout the entire respiratory cycle suggesting either a foreign body in the trachea or any condition that would produce partial obstruction to both main bronchi.

At bronchoscopy a large quantity of thick mucoid secretion was removed from the trachea and both main bronchi. There was no evidence of aspirated foreign body. A roentgen study made following bronchoscopy indicated that there was a marked decrease in the degree of overdistention of the lungs. Wheezing and dyspnea were absent. There was roentgen evidence of nasal accessory sinus disease. Skin tests were carried out and were found positive for two foods, namely chicken and beef. Their use, however, did not produce symptoms. On close questioning it was learned that this patient had slight dyspnea lasting for about one hour three weeks previously. Treatment of the sinuses has since been carried out and the patient has had only occasional slight attacks of wheezing.

It is believed that in both of these groups, one occurring in adults, the other in children, there was an intrinsic cause for the asthmatic attacks. Sinus disease was present in a majority of cases.

In the first group there was found evidence of a chronic infection of the

mucosa of the tracheobronchial tree. Treatment of the sinus infection when present and attempts at desensitization gave slight relief and to only a few cases. Bronchoscopy with removal of secretions gave prompt relief. When bronchoscopy was repeated at intervals the attacks either did not recur or produced only slight distress.

In the second group the findings suggested an acute inflammatory process. Bronchoscopic aspirations afforded prompt temporary relief. Treatment of a sinus infection when present gave the best ultimate results.

It is difficult to state how bronchoscopy is helpful in these cases unless it is the result of removal from the bronchi of thick secretions that interfere mechanically with the exit of air during expiration. There can be no question that bronchoscopy is of value. If the symptoms are the result of simple mechanical obstruction of bronchi one would expect patients with extensive bronchiectasis to exhibit symptoms of bronchial asthma. The occurrence of obstructive emphysema and particularly a patchy obstructive atelectasis undoubtedly exerts an influence although this is difficult to prove. Lobal atelectasis as a complication of asthma has been described by Clarke and others. It was my privilege to observe Clarke's case bronchoscopically. The bronchoscopic observations made did not permit one to arrive at definite conclusions.

The coexistence of asthma with bronchiectasis is not frequent, although I believe that it is more common than medical literature indicates. It is probable that the asthma antedates the bronchiectasis. In spite of this, however, the asthmatic attacks are more frequent and severe when the bronchiectasis does not drain properly. The presence of bronchiectasis can be positively determined only by the introduction into the bronchial tree of iodized oil. Although this has been done in a number of cases without untoward results one death did follow its use. This patient, a woman, had frequent paroxysms of severe asthma for many years. There was evidence of bronchopulmonary disease. During the bronchoscopic aspiration of secretion she developed a paroxysm of asthma, about 9 cc of iodized oil were instilled into each of the lower lobe bronchi. Dyspnea increased and death ensued within 20 minutes. The cause could not be determined. No autopsy was permitted and it was not learned if bronchiectasis was present. Since bronchoscopy affords the best opportunity for the collection of material for the preparation of autogenous vaccines a word of comment on the use of such vaccines may be added at this point. The empiric use of autogenous vaccines in asthma may not be considered wholly scientific when there is doubt concerning the exciting factors. In spite of this, however, satisfactory results have been secured from such vaccines in a sufficiently large percentage of obscure cases of asthma to warrant their employment. In a previous communication I reported a case of asthma that secured complete relief of symptoms from the use of vaccine made from bronchoscopically removed secretions. This patient had been treated by several competent allergists without benefit. Two additional cases have now se-

cured complete relief following the use of autogenous vaccines. I believe therefore that they should be employed in selected cases.

SUMMARY

Bronchoscopy is of value in the study of certain clinical conditions described as bronchial asthma. No allergy or asthma clinic is complete without the services of a competent bronchoscopist.

Bronchoscopy should be given a trial in the treatment of cases of bronchial asthma that do not respond to commonly employed methods. The best results are secured in cases with tracheobronchitis, excessive secretions or bronchial obstruction.

Vaccines made from bronchoscopically removed secretions are of value in cases of so-called bacterial allergy.

BIBLIOGRAPHY

- BROWN, G. T. The diagnosis of bacterial allergy, *South Med. J.*, 1934, **xxvii**, 856.
- CLARKE, J. A., JR. Pulmonary atelectasis as a complication of bronchial asthma, *Arch. Int. Med.*, 1930, **xliv**, 624.
- CLERF, L. H. Bronchoscopy as an aid in diagnosis and treatment of bronchial asthma, *Jr. Am. Med. Assoc.*, 1927, **lxviii**, 872.
- FLETCHER, G. W. Asthma from the standpoint of the rhinologist, *Manitoba Med.*, 1935.
- HALLIDAY, A. A. On the bronchoscopic method of diagnosis and treatment of certain disorders of the lungs and bronchi, *Canad. Med. Assoc. J.*, 1927, **xxii**, 561.
- JACKSON, C. Chronic nonspecific infection of the lungs, *Jr. Am. Med. Assoc.*, 1926, **lxvii**, 727.
- KERN, R. A. Problems in diagnosis and treatment of bronchial asthma and hay fever, *Atlantic Med. J.*, 1926, **xxix**, 334.
- LUKENS, R. M. Bronchoscopy in the treatment of asthma, *Laryngoscope*, 1925, **xxxv**, 227.
- MOORE, W. F. Ciliary inhibition or destruction in tracheobronchial asthma, *Am. Jr. Med. Sci.*, 1925, **clxiv**, 799.
- WEILIE, F. L. Studies in asthma, *New Eng. Jr. Med.*, 1931, **ccv**, 848.

PROGNOSIS IN ACUTE GLOMERULAR NEPHRITIS

By ARTHUR B. RICHTER, M.D., *Boston, Massachusetts*

THE outlook for adults who have acute glomerular nephritis has seldom been the subject of comment in the literature. Excepting war nephritis, the few studies on prognosis are mostly in children. The mortality during the acute stage of the disease is regarded as low in both groups, but both the immediate and the late prognosis are apparently more favorable in the earlier ages. However, the death rate during the acute stage in the cases of acute nephritis, chiefly adults, recently reported by Murphy, Grill and Moxon¹ was so high as to challenge the truth of these beliefs.

The present study was undertaken to determine what had been the experience at the Peter Bent Brigham Hospital in this regard. One hundred cases of typical, acute, diffuse glomerular nephritis were selected from 160 so diagnosed during the years 1913 to 1934 and the ultimate outcome determined by a follow-up study which was successful in disclosing the renal condition of all but 13 of the 90 individuals who survived their acute illness. The data are extraordinarily complete because of the constant interest in the disease shown by Dr. J. P. O'Hare and Dr. Henry A. Christian. Sixty cases were rejected because of one or more features which suggested that they were probably instances of chronic nephritis with acute exacerbation. All but one of the cases were observed in the hospital for an average of six weeks during their acute process, and the one exception was treated at home by Dr. O'Hare. It was, therefore, possible to observe almost all of the patients throughout the early stages of their disease.

Acute Stage. As can be seen in table 1, there were twice as many males as females. The age incidence varied from 12 to 59 years, the former being the lowest age limit for admission to the medical service of this hospital.

Acute nephritis is most common in children and young adults. This is the period of life when the causative acute infections of the upper respiratory tract are most frequent. Three-fourths of this series were between 12 and 30 years, only seven were above 40 years.

Ten patients died during the acute stage. In five, death was not attributed to the nephritis but to the causative infection, or to an incidental factor such as acute syphilitic meningitis, broncho-pneumonia, lobar pneumonia, hemorrhage from carcinoma of the cecum, and generalized peritonitis from perforation of a typhoid ulcer. Of the five patients whose death was due primarily to acute nephritis, four were in the third decade and one in the sixth. Three died of uremia, one of broncho-pneumonia and severe fatty degeneration of the liver, and one of erysipelas. The complicating

* Received for publication July 27, 1935.

From the Medical Clinic of the Peter Bent Brigham Hospital. Aided in part by the Fund for Research in Renal and Vascular Diseases.

TABLE I

Age and Sex Incidence in 100 Cases of Acute Nephritis with Outcome in Relation to Age

Age, Years	Number of Cases	Females	Males	Died of Acute Nephritis	Died of Etiologic Disease or of Incidental Cause	Became Chronic	Cured	Renal Condition Unknown
12-20	39	14	25	0	1	5	28	5
21-30	35	12	23	4	2	7	18	4
31-40	19	6	13	0	0	3	12	4
41-50	4	1	3	0	0	0	4	0
51-60	3	0	3	1	2	0	0	0
Total	100	32	68	5	5	15	62	13

diseases in the last two cases developed about two weeks after the onset of acute nephritis

The etiologic factors, as can be seen in table 2, are similar to those given by others^{2, 33}. Infections of the upper respiratory tract, including tonsillitis, pharyngitis, peritonsillar abscess, the common cold, and otitis media, accounted for 66 per cent, while in 15 cases, an etiologic factor could not be

TABLE II

Etiology of 100 Cases of Acute Nephritis with Relation to Outcome

Etiology	No of Cases	Died of Acute Nephritis	Died of Etiologic Disease or of Incidental Cause	Cured Cases	Became Chronic	Renal Condition Unknown
Sore throat, tonsillitis	28	1	2	20	3	2
Common cold, grippe (Associated with sinusitis, pleurisy, cervical adenitis, or rheumatic fever—4 cases)	27	1	1	18	4	3
Peritonsillar abscess	9	2	0	3	1	3
Pneumonia (lobar—4 cases)	5	0	1	2	2	0
Scarlet fever	4	0	0	3	0	1
Cold (exposure)	3	1	0	2	0	0
Typhoid fever	2	0	1	1	0	0
Otitis media	2	0	0	2	0	0
Erysipelas	1	0	0	1	0	0
Mumps	1	0	0	1	0	0
Purpura	1	0	0	0	1	0
Rheumatic fever	1	0	0	1	0	0
Influenza and empyema	1	0	0	0	0	1
Unknown	15	0	0	8	4	3
Total	100	5	5	62	15	13

determined. The onset of acute nephritis followed scarlet fever in only four patients. The infrequency of postscarlatinal nephritis in this series is probably due to the fact that cases of scarlet fever are rarely admitted to this hospital. Three of the four cases of postscarlatinal nephritis occurred in brothers at about the same time, and could be classified as cases of so-called familial nephritis.³ These three are now cured, 16 years later. The remaining case did not return for follow-up study. Lobar pneumonia (in four cases), and broncho-pneumonia (in one) accounted for 5 per cent of the cases of acute nephritis. Rheumatic fever is rarely the cause of true glomerular nephritis,⁴ but it is the attributed cause in one of our cases. Another patient, following his second attack of rheumatic fever accompanied by an acute upper respiratory tract infection, developed acute nephritis which was believed due to the latter infection. The urine of this patient had not cleared at the end of three weeks, and he died of influenza a few months later. Mumps is not usually considered a cause of acute nephritis, however, one patient, aged 20, following an attack of epidemic parotitis, developed typical acute glomerular nephritis. Although the urine had not cleared during four months of observation, 14 years later there was no evidence of chronic nephritis.

Table 3 shows the frequency of the various symptoms and signs. Significant early symptoms and signs of acute nephritis may be absent, the

TABLE III
Symptoms and Signs in 100 Cases of Acute Nephritis

Symptoms and Signs	Per cent	Symptoms and Signs	Per cent
Albuminuria	100	Diarrhea	3
Microscopic hematuria	87	Constipation	3
Edema	65	Anuria	3
Gross hematuria	42	Dyspnea	3
Headache	18	Coma	3
Nausea and vomiting	15	Pain in epigastrium	3
Oliguria	11	Transient blindness	2
Backache	10	Mental confusion	2
Convulsions	9	Dizziness	1
Frequency of urination	6	Pains in joints	2
Fatigue	6	Purpura	1
Dysuria	3	Congestive heart failure	1

diagnosis being incidental to a routine urine examination. This was true in 14 of our cases. Edema, non-uremic convulsions, hypertension, neuro-retinopathies, myocardial failure, uremia, gross hematuria, and albuminuria were the only signs which seemed possibly related to the outcome of the nephritis.

Edema which occurred in two-thirds of both the cured and the chronic cases was usually confined to puffiness about the eyes and swelling of the ankles. There was no relationship between the degree or duration of edema and prognosis. As is usually true in acute nephritis, the amount of total protein, albumin and globulin of the blood was normal, or but slightly lowered, in the few cases in which these determinations were made.

Hypertensive encephalopathy manifested as convulsive seizures is not uncommon in acute nephritis, especially in children. Of the 100 cases, nine between the ages of 12 and 37 years had convulsions. All of them had hypertension and a normal or only slightly elevated blood urea nitrogen. In seven, the convulsions were due to hypertensive encephalopathy, while there was probably another cause in the other two. One of these died of acute syphilitic meningitis about two weeks after the onset of acute nephritis. The other patient is most interesting. The convulsions, first occurring at the onset of his acute nephritis, persisted periodically until death about eight years later. Although the nephritis became chronic, the blood pressure and kidney function remained normal. The true cause of the convulsions became evident with the development of more definite signs of brain tumor, which proved to be a glioma of the frontal lobe (no 8, chart 2). The seven cases of hypertensive encephalopathy recovered and are now without evidence of chronic nephritis five to 14 years later.

Hypertension was present in 53 of the 96 cases in which the blood pressure was recorded (table 4). Its occurrence was twice as frequent in the

TABLE IV
Range of Blood Pressure in 96 Cases of Acute Nephritis

	Systolic Pressure	Diastolic Pressure		
	180-200	105-200	90-100	60-85
Number of cases	10	5	4	1
	150-175	105-200	90-100	60-85
Number of cases	27	8	15	45
	100-145	105-200	90-100	60-85
Number of cases	59*	4	12	43

* 16 cases had normal systolic and elevated diastolic pressures

patients who were seen within two weeks of their first symptoms of nephritis as in those admitted later. This suggests that hypertension tends to occur early in the disease, and that possibly the former group were brought to the hospital earlier because of a more severe form of nephritis. The presence of hypertension was unrelated to the outcome. The general rule that a gradually rising blood pressure, or hypertension, persisting longer than a few days is an unfavorable sign in acute nephritis was borne out in the two cases in which it was applicable. One died in the acute stage, the other developed chronic nephritis. Only one of the three patients who died of uremia had hypertension, and this was minor.

Slight neuro-retinopathy consisting of edema of the disc and retina, and constriction of the retinal arteries, was observed in three cases of the series all of which recovered.

Myocardial insufficiency, an important feature in a very small proportion of cases of acute nephritis, is at times precipitated during convulsive seizures. Cardiac failure did not, however, result from this cause in our series, although two patients had frequent severe convulsions for 24 hours before entry. Congestive failure, of moderate degree, occurred in only one case,

while dyspnea, which may have been due to left heart failure, was a symptom in three more. These four patients recovered.

All of the 100 cases had albuminuria as determined by the nitric acid test. The urinary sediments of 87 contained moderate to large numbers of red and white blood cells. In 13 there was only an occasional red blood cell during the period of observation, but more blood was probably present prior to entry to the hospital. In this clinic, the presence of red blood cell casts has been used as an important aid in distinguishing nephritis from other causes of hematuria. They were fairly constantly present in the early stage of the nephritis in the majority of the cases.

Neither the presence nor the severity of gross hematuria, which occurred in 42 per cent of the cases, was related to the outcome of the nephritis.

It is well known that renal function determined by the usual tests is of little significance in most cases of acute nephritis. This is partly due to the transient nature of the early injury in otherwise normal kidneys. During the period of anuria and oliguria the phenolsulphonephthalein excretion and urea clearance are diminished, and the blood urea nitrogen is elevated.^{5, 6} This was found to be true in our series. Azotemia, present in 49 of 90 cases, was slight in most of them, and it usually occurred early in the nephritis. The blood urea nitrogen ranged from 16 to 180 mg per 100 cc (table 5). The three patients who died of uremia had anuria and a urea

TABLE V

Range of Blood Urea Nitrogen in 49 Cases of Acute Nephritis with Azotemia

Milligrams per 100 cc	Number of Cases
16-30	22
31-40	12
41-60	7
61-90	5
120-180	3

nitrogen of more than 120 mg per 100 cc. The phenolsulphonephthalein excretion was determined in most of the series. The urea clearance was determined less often than the dye test, but in the cases in which both were done, the information obtained was of as little prognostic value as from the dye test alone. This may be in part explained by too infrequent use of the tests, since it is well known that it is the trend of repeated tests over a period of time, and not the single test, regardless of the kind, which gives the most useful indication of kidney function.

Late Prognosis. Most of the patients returned to the renal clinic, under the direction of Dr. O'Hare. In a few the data necessary to determine the presence or absence of chronic nephritis were obtained from the patient's physician. The criteria for complete recovery from acute nephritis consisted of normal kidney function tests, negative urine examinations and normal blood pressure. However, two cured cases, who developed hypertension about 10 years after their acute nephritis 19 years ago, have shown no evi-

dence of chronic nephritis. The blood pressure of one of them has been normal since an attack of coronary thrombosis three years ago.

Eighty-one of the 90 who survived their attack of acute nephritis have been traced. The renal status of 77, or 85.5 per cent, has been determined at periods varying from 1 to 19 years after the onset of acute nephritis (table 1). The average follow-up period was 8.7 years. Of the 13 patients whose renal condition was undetermined, nine could not be found, two had died of influenza a few months following the onset of acute nephritis, and one had died of pulmonary tuberculosis 15 years later, the renal condition being unknown. The last, who is still living after 17 years, did not respond to our inquiries. Of the 77 patients whose renal condition is known, 62, or 80.5 per cent, are cured, while 15, or 19.5 per cent, have developed chronic nephritis.

Albuminuria is the most delicate evidence of the presence of nephritis.⁵ We have, therefore, as presented in charts 1 and 2, given special attention to the duration of albuminuria as a possible aid in prognosis. Of the 62 cured cases, the urine was known to have become free of albumin within two months in 14, within six months in 13, within 10 months in 4, and within a year in nine cases. The urine became albumin-free after one year in four cases, 1.5 years in one, and two years in two. The approximate time when the urine cleared in 15 patients could not be determined because of infrequent visits to the clinic. In other words, the urine became albumin-free in about half of the 62 cured cases within six months, between six months and a year in one-fifth and later than a year in one-ninth. Two patients (nos 8 and 24, chart 1) demonstrate the significant fact that acute nephritis may heal after albuminuria has been present for two years. It is quite possible that three cases (nos 13, 14 and 15, chart 2), now considered as having chronic hemorrhagic nephritis at 19 months in one case, and two years in the other two, may be found without evidence of nephritis in a longer follow-up study.

Of the 15 patients who developed chronic nephritis, the first 12, as shown in chart 2, were followed from 3 to 19 years. In eight of these, albuminuria in constant or increasing amounts was present on all examinations during the first year, and thereafter. Five of the eight developed chronic, hemorrhagic nephritis, and four of them were followed regularly until death. Two died in uremia five and eight years, respectively, after the onset of acute nephritis (nos 9 and 10). The other two, whose blood pressure and kidney function tests remained normal, died of incidental causes three and four years later (nos 8 and 12). The fifth patient (no 1) was not seen between the first and third years after the onset of acute nephritis, but returned regularly thereafter, at 19 years albuminuria was present but the blood pressure and kidney function tests were normal. Three of the eight cases in which albuminuria was present during the first year were followed less regularly than the five discussed above. The first (no 3) did not return after the first year, at the end of 16 years death was caused by uremia or cerebral hemorrhage. The second (no 6) had hypertension at three years.

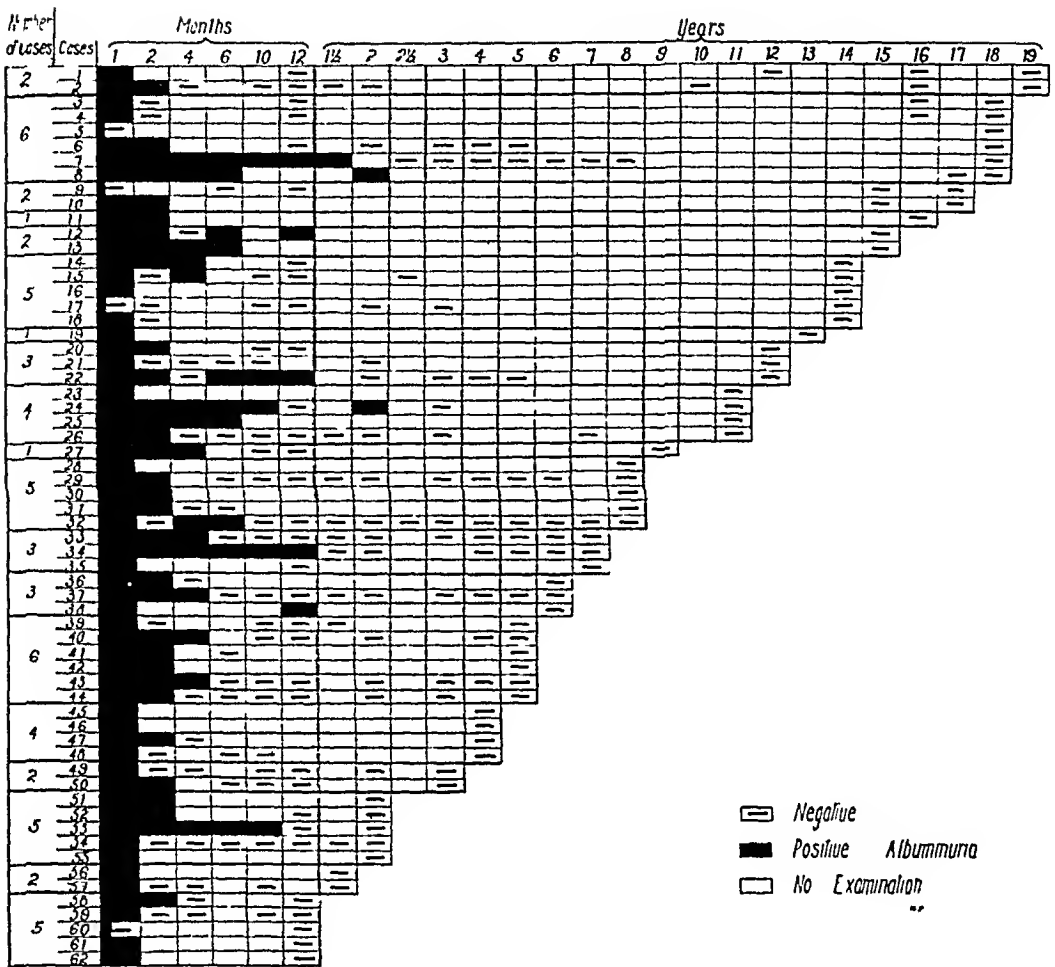


CHART 1 Showing urinary examinations of 62 patients who are cured of acute nephritis

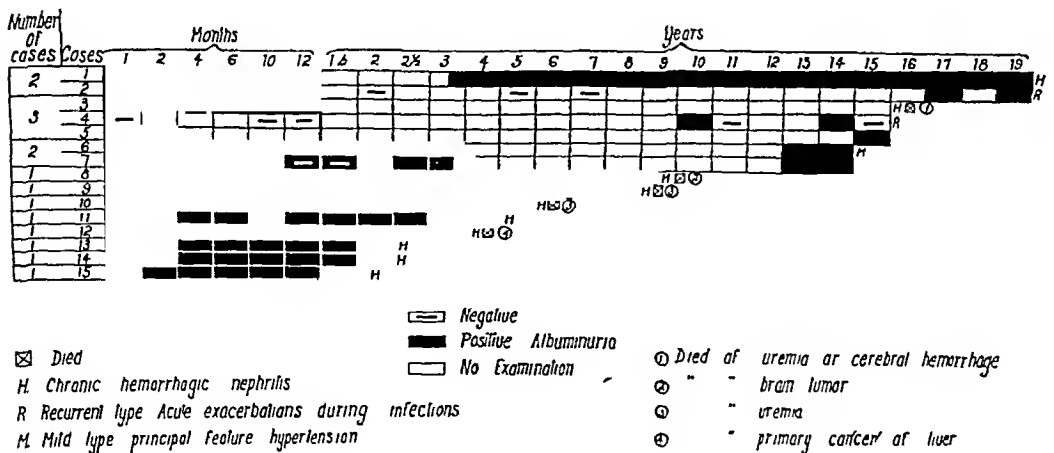


CHART 2 Showing urinary examinations of 15 patients who developed chronic nephritis

During the next nine years he was not seen at all, on his return, 13 and 14 years after the acute nephritis, the hypertension had increased. Although albuminuria and cylindruria were still present, various kidney function tests were normal. The heart was not enlarged on roentgen examination. There was moderate generalized arteriosclerosis. The third (no 2) was not observed between the first and second years after acute nephritis. He did, however, report to us later. The urine was negative at two years, positive for albumin and casts 10 months later, negative at five and seven years, and again positive at 17 and 19 years. Kidney function tests and the blood pressure were normal at all examinations. Moderate generalized arteriosclerosis was present.

In only two of the 15 chronic cases did the urine become negative within a year, during the first month in one of them. The latter case (no 4) was not seen from the first to the tenth year. An acute exacerbation of the chronic nephritis occurred during an acute infection of the upper respiratory tract at 10 and 14 years after the initial attack of acute nephritis. This patient would have been considered cured had he not been seen during the acute exacerbation. The other patient (no 7) had negative urine examinations between the first and second years, but at two years albuminuria and hematuria recurred. He was treated for pulmonary tuberculosis 10 years later when there was still evidence of chronic nephritis. The tuberculosis became arrested and he is now reported to be well.

The urine studies of five cases with chronic nephritis were too infrequent to be of value in estimating the significance of albuminuria. Case 5 was observed for two months after the onset of acute nephritis, 15 years later he was reported to have albuminuria, hypertension, and cardiac enlargement. In case 11 the acute nephritis progressed into chronic, hemorrhagic nephritis, the blood pressure and kidney function tests were normal during the four years he was followed. Cases 13, 14 and 15 have chronic, hemorrhagic nephritis with normal blood pressure and kidney function tests, about two years following the initial stage.

A comparison of charts 1 and 2 shows that 80 per cent of the regularly followed cases, in which chronic nephritis developed, had albuminuria one year after the onset of acute nephritis, while only 14.8 per cent of the cured cases had albuminuria at the end of the first year or later. In other words, when albuminuria was still present at the end of a year or thereafter, the chances for progression of the nephritis into the chronic stage were approximately 6 to 1.

Significant features not given in the charts are the presence of hematuria and cylindruria, and the degree of albuminuria. Hematuria and cylindruria, often occurring in the absence of albuminuria, were important signs of renal activity, but because of their intermittent occurrence and quantitative variation, the degree and duration of albuminuria served as a more useful indication of the general trend of the course of the nephritis. In each of the 62 patients who became cured, there was either a gradual or intermittent de-

crease in the amount, or complete disappearance of the albuminuria over a period of a few weeks up to two years after the onset of acute nephritis. In the 10 chronic cases who were examined regularly during the first year, there was a slight, early decrease of the albuminuria while the patients were at bed rest, but by two months and thereafter the degree of albuminuria was constant or increasing.

In only one patient did the acute nephritis progress rapidly so that hypertension had developed by the end of one year.

The patients, in our clinic, with the nephrosis syndrome were not observed during the initial stage of their nephritis, therefore, this complication was not present in any of the cases followed in the present study.

Orthostatic albuminuria was present in only one patient, six years after the attack of acute nephritis.

Comment. A study of table 6, in which the cases of Murphy and his

TABLE VI
Statistics on the Prognosis of Acute Glomerular Nephritis in Adolescents and Adults

Author	Immediate Prognosis			Late Prognosis			
	Age Group in Years	No of Cases	Died of Acute Nephritis, Per cent	No of Cases in Follow-Up Study	Average Follow-Up in Years	Cured, Per cent	Became Chronic, Per cent
Murphy, Grill and Moxon	82 cases above and 12 below 11 years	94	28.7	*94	Not given	50	21.2
				*67 surviving acute stage	" "	70.1	29.8
†Murphy et al revised	11-60	82	30.5	*82	" "	48.7	20.7
				*57 surviving acute stage	" "	70.1	29.8
McPhee and Kaye	67 cases above and 23 below 11 years	90	5.5	48	4.5 to 7.3	85.4	14.6
†McPhee revised	11-70	67	7.5	28	4.5 to 7.3	75	25
Ernberg	15-30	—	—	16	Several years	75	25
P B B H Series	12-60	100	5.†	*100	8.7	62	15
				*77§ surviving acute stage	8.7	80.5	19.5

* Calculated on basis of

† Cases arranged into group comparable to that of P B B H Series

‡ Five other cases died of causative infection or of incidental causes

§ Renal condition of 13 cases is unknown

co-workers, and of McPhee and Kaye⁷ have been classified into an age group corresponding to the 100 cases of the present study, shows the death rates during the acute stage of 31.7 per cent in Murphy's series, 7.5 per cent in that of McPhee and Kaye, and 5 per cent in our series. In the cases of acute glomerular nephritis in children, reported by Tallerman,⁸ Guild,⁹ Lyttle and Rosenberg,¹⁰ Osman,¹¹ Hill,¹² and Blackfan,¹³ the death rates during the acute stage ranged from 3.3 to 12.5 per cent, with an average of 6.6 per cent. The mortality, in the acute stage of war or trench nephritis, was slightly lower than in the acute glomerular nephritis of childhood, or in civilian nephritis of adults. Reports of cases of war nephritis by various authors^{14 to 21} gave death rates during the acute stage ranging from 0.8 to 7.6 per cent, averaging 3.6. In the literature the greatest variation in death rates in acute nephritis was found in the reports of various small series of postscarlatinal nephritis, where the virulence of an epidemic appeared to be a factor. However, in a large series of postscarlatinal nephritis in children and young adults, reported by Hansborg,²² the death rate was 4 per cent, and 6 per cent in a similar series of Barasch.²³ This review of the literature and the study of our cases not only bears out the opinion that the immediate prognosis in acute glomerular nephritis is good, but also shows that there is no essential difference in the death rate in children and adults, except in trench nephritis where the mortality was lower than in either children or adults in times of peace. The mortality of 28.7 per cent in the series of Murphy, Grill and Moxon is the highest found in the literature. The deaths in their series did not seem attributable to the disease which caused the nephritis.

A comparison of the late prognosis in acute nephritis of adults is also shown in table 6, in which the cases of Murphy and of McPhee and Kaye have been classified into age groups, similar to that of our series. The percentage of cases in our group which developed chronic nephritis is a little lower than in the adult cases of the other authors. In acute glomerular nephritis in children, reported by various authors,^{5, 6, 7, 9, 24, 25, 26, 27} the percentage of cases which became chronic varied from 0 to 16, indicating a more favorable remote prognosis than in adults. The high incidence of 51.8 per cent in the series of Patterson and Wyllie,²⁸ and 35.7 per cent in Osman's¹¹ series of children and young adults, was unexplained. The various reports of postscarlatinal nephritis gave a definitely lower incidence of progression into chronic nephritis than in nephritis of mixed etiology. In the reports of acute war nephritis,^{15, 16, 18, 29, 30} the percentage of cured cases ranged from 45 to 85. The number of cases which developed chronic nephritis is difficult to evaluate because of their grouping by some authors into cases which developed chronic nephritis, cases with "residual albuminuria" without signs of nephritis, and "cases of contracted kidney with retinal and vascular degeneration." The various authors writing about war nephritis have, however, believed that a greater proportion of these cases

developed chronic glomerular nephritis than in civilian nephritis, for which a satisfactory explanation has not been given

The present group includes both severe and mild cases of acute, diffuse, glomerular nephritis caused by various acute infections

The only clinical observation frequently related to the ultimate outcome of the nephritis was the degree and duration of albuminuria. Similar observations described by others have rarely been expressed statistically. Brown and Evans³¹ stated that the disappearance of albuminuria within a month after the onset of acute nephritis is a hopeful prognostic sign, while Tidy³² believed that the development of chronic nephritis is usual if albuminuria persists longer than a month. Fishberg³³ makes the statement that the longer albuminuria persists the greater the chances of the nephritis becoming chronic. Murphy¹ believed that gradually diminishing albuminuria points toward a healing process. In the majority of her cured cases of acute glomerular nephritis in children, Guild found the urine cleared promptly, within two months in most cases, but that albuminuria persisted for many months in a few. Addis,³⁴ by use of his sediment counts, and quantitated proteinuria, has shown that in three-fourths of the cases of acute, hemorrhagic nephritis healing occurs during the first year, but complete recovery occurred as late as the fifth year.

The results in our cases suggest that when albuminuria had persisted for a year or longer after the onset of the acute nephritis, the chances of the process becoming chronic were six to one.

It should be emphasized that clinical cure of acute nephritis may not always represent cure of the underlying pathologic process. This is well illustrated by the rare case (case 4, chart 2) in which the nephritis is manifest only during exacerbations following acute infections, the urinary and kidney function studies being entirely normal in the interim. When the intervals between observations or the exacerbations are long, or if antecedent flare-ups are unknown, such a case might easily be considered cured of the initial nephritis, if not followed for a very long time. In a clinical study of this kind such a possibility cannot be eliminated.

For the purpose of this study we have considered a patient cured if there was no evidence of nephritis at the end of one year. The validity of this is borne out by the fact that of the 42 cases apparently cured at one year (average 8.7 years), only two have been found to have chronic nephritis at a later date.

SUMMARY

Of 100 adolescents and adults with acute diffuse glomerular nephritis, 10 died during the acute stage, five primarily of their nephritis, and five of the causative infection, or of incidental causes. Eighty-one of the surviving 90 have been traced and the renal status determined in 77. Sixty-two are cured, and 15 have developed chronic nephritis during the follow-up periods, which were from 1 to 19 years with an average of 8.7 years.

The relation of the various clinical features to prognosis is discussed. The one clinical observation of greatest prognostic value was the degree and the duration of albuminuria. In the majority of the cases, disappearance or gradual and intermittent decrease in the amount of albuminuria indicated healing of the nephritis, while persistent albuminuria of a constant or increasing amount suggested progression into chronic nephritis. The results also suggest that when albuminuria (orthostatic factor excluded) persists for a year or longer after the onset of acute nephritis, the chances of the renal process becoming chronic are six to one.

REFERENCES

- 1 MURPHY, F. D., GRILL, J., and MOYON, G. F. Acute diffuse glomerular nephritis, study of 94 cases with special consideration of the stage of transition into the chronic form, *Arch Int Med*, 1934, lrv, 483.
- 2 LONCOPE, W. T. The pathogenesis of glomerular nephritis, *Bull Johns Hopkins Hosp*, 1929, xlv, 335.
- 3 ERNSTENE, C. A., and ROBB, G. P. A familial epidemic of acute diffuse glomerulonephritis, relation to the pathogenesis of the disease, *Jr Am Med Assoc*, 1931, xcvi, 1382.
- 4 BALHR, G., and SCHITRIN, A. The rarity of glomerulonephritis in rheumatic fever and its significance, *Libman Ann Vols*, 1932, i, 125.
- 5 CHRISTIAN, H. A., and O'HARE, J. P. Nephritis, *Oxford Medicine*, Vol. 3, Part II, 582.
- 6 O'HARE, J. P. Diseases of the kidney, *Nelson Loose-Leaf Medicine*, 1931, iv, 651.
- 7 MCPHEE, I. M., and KAYE, G. Some observations on the prognosis in acute nephritis, *Med Jr Australia*, 1932, ii, 14.
- 8 TALLERMAN, K. H. Prognosis in acute nephritis in childhood, *Lancet*, 1932, ii, 60.
- 9 GUILD, H. G. Acute glomerular nephritis in childhood, *Bull Johns Hopkins Hosp*, 1931, xlviii, 193.
- 10 LYTTLE, J. D., and ROSENBERG, L. Prognosis of acute nephritis in childhood, *Am Jr Dis Child*, 1929, xxxviii, 1052.
- 11 OSMAN, A. Etiology and prognosis of nephritis in children and young adults, *Guy's Hosp Rep*, 1925, lxxv, 306.
- 12 HILL, L. W. Studies of nephritis in children, II, *Am Jr Dis Child*, 1919, xvii, 270.
- 13 BLACKFAN, K. Acute nephritis in children, *Bull Johns Hopkins Hosp*, 1926, xxxvi, 74.
- 14 MACLEAN, H. Albuminuria and war nephritis among British troops in France, *Med Res Council, Special Report Series*, No. 43, London, 1919.
- 15 KEITH, N. M., and THOMSON, W. D. War nephritis, a clinical, functional and pathological study, *Jr Urol*, 1919, iii, 87.
- 16 TOENNIEN, E. Klinische und funktionelle Beobachtungen über die Feldnephritis und ihre Verwertung für die allgemeine Pathologie der Niere, *Deutsch Arch f klin Med*, 1919, cxix, 183-207.
- 17 HUME, W. E., and NATTRASS, F. J. Late effects of war nephritis, *Quart Jr Med*, 1927, xxi, 1.
- 18 GROS, A. Zur Prognose der akuten Nephritis, *München med Wchnschr*, 1929, lxxvi, 655.
- 19 DYKE, S. C. More remote prognosis in war nephritis, *Quart Jr Med*, 1922, xv, 207.
- 20 SIGURET, G. Enquête sur 47 cas de nephrites de guerre, *Arch Med-Chir de Province, Tours*, 1923, xiii, 152.
- 21 SCHIROKAUER, H. Über den Ausgang der sogenannten Kriegsnephritis, *Med Klinik*, 1920, xvi, 845.

- 22 HANSBORG, H Untersuchungen über die Prognose der Scharlachnephritis, Acta Med Scandinav, 1925, *lx*, 570
- 23 BARASCH, H Zehn Jahre Scarlachstatistik, Deutsch med Wchnschr, 1915, *xl*, 4
- 24 ERNBERG, H Über akute Nephritis in den Kinder und Jugendjahren mit besonderer Berücksichtigung der Prognose, Nord Med Arch, 1911, *xliv*, 109
- 25 BOYD, G L Acute nephritis in children, Canad Med Assoc Jr, 1927, *xvii*, 895
- 26 CLAUSEN, S W Nephritis in children, Atlantic Med Jr, 1926, *xxix*, 201
- 27 JAMES, R F Prognosis of nephritis in children, Jr Am Med Assoc, 1921, *lxxvi*, 505
- 28 PATTERSON, D, and WYLLIE, W G Nephritis in children, its prognosis, Arch Dis Child, 1926, *i*, 103
- 29 DEUTSCH, F Kriegsnephritikerschicksale, Med Klinik, 1921, *xvii*, 1318-1321
- 30 GERHARDT, D Über Ausgangsweisen der Kriegsnephritis, München med Wchnschr, 1919, *vi*, 145
- 31 BROWN, W L, and EVANS, G A textbook of the practice of medicine, quoted by McPhee and Kaye,⁷ 1926, 1161
- 32 TIDY, H L Synopsis of medicine, 1924, J Wright and Sons, London, 569
- 33 FISHBERG, A M Hypertension and nephritis, 3rd Ed, 1934, Lea and Febiger, Philadelphia
- 34 ADDIS, T Hemorrhagic Bright's disease I Natural history, Bull Johns Hopkins Hosp, 1931, *xliv*, 203

THE EFFECTIVENESS OF THE SIPPY REGIMEN IN NEUTRALIZING THE GASTRIC JUICE OF PA- TIENTS IF THE AMOUNT OF ALKALI IS NOT VARIED *

By PAUL H. WOSIKA, M.D.,[†] *Chicago, Illinois*, and EDWARD S. EMERY,
Jr., M.D., *Boston, Massachusetts*

THE method of ulcer treatment as suggested by Sippy is frequently used in the belief that placing the patient on the routine as outlined will effect complete neutralization of the gastric contents. Some may question the necessity of maintaining neutrality in the stomach, or may even doubt that neutrality provides optimum conditions for healing. Sippy himself, however, suggested that the absence of free acid should be used as a criterion for the effectiveness of treatment, and this conception appears to have been commonly adopted in theory. We have been unable to find in the literature any data giving hourly values for gastric acidity in patients on unmodified Sippy management. The present study has been undertaken to determine how often the unmodified regimen will bring about complete neutralization.

METHOD OF STUDY

A representative group of 55 patients with peptic ulcer has been studied. Forty-six were suffering from duodenal and nine from gastric ulcer. Their ages varied from 20 to 70 years, the average age for the entire group being 44 years. Forty-eight were males and seven females. All of the patients were having symptoms of peptic ulcer at the time of entrance into the hospital. All but one showed a typical deformity with the roentgen-ray, and in most instances, a crater was demonstrated fluoroscopically. The one exception had such a typical history that the diagnosis of peptic ulcer seemed definite in spite of the negative roentgenographic studies. Because the number of gastric ulcers is small, we did not include them in our data. However, the findings in these patients were similar to those obtained in cases of duodenal ulcers.

No postoperative cases were used because of the difficulty encountered in determining the site of the tube in the stomach. Furthermore, it was thought that the data obtained on postoperative stomachs might be misleading in so far as the purposes of this study are concerned.

Patients were placed on the routine treatment as outlined by Sippy. They were started on 90 c.c. of equal parts of whole milk and 20 per cent cream on the hour, from 7 a.m. to 7 p.m. They were given a powder consisting of calcium carbonate (0.6 gm.) and sodium bicarbonate (2.0 gm.)

* Received for publication July 15, 1935.

From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.

[†] The investigation was aided by a grant from the Upjohn Company, Kalamazoo, Mich.

on the half hour. This procedure will be referred to in the remainder of the paper as the "first day Sippy." Increasing amounts of food were given in the succeeding days so that by the seventh day, patients were also receiving six small feedings of soft eggs, cereals, toast, crackers, butter, and jellies at two hour intervals. Studies were made on the first or second day after the patient was taking all six feedings. This period of study will be later referred to as the "seventh day Sippy." Two weeks later the diet was changed to the so-called "fourth week Sippy." Three small meals were substituted for the six feedings. Milk and cream and powders were continued as before. These meals included a wide variety of foods, although all vegetables and fruits were either strained or pureed. Relishes and highly seasoned food were forbidden. The patients were allowed out of bed and were encouraged to engage in as much activity as ward life would permit.

The patients were studied on the "first day," "seventh day," and "fourth week" periods. Because many physicians have disapproved of giving the amounts of alkali required by the Sippy regimen on the grounds that it tends to increase the production of hydrochloric acid and, therefore, defeats the purpose of the treatment, as well as producing alkalosis on occasion, we have also determined the effect of taking milk and cream without powders. Unless the patients were extremely ill, this procedure was carried out before the Sippy regimen was begun. This was done to avoid the possible cumulative effect of previous alkalis on the gastric response.

The routine on the days of study was as follows: a Levine tube was passed at 7 a.m. and the total fasting secretion was removed. Five c.c. specimens were withdrawn at intervals of 30 minutes throughout the day, just prior to the administration of milk or powders. The specimens were examined promptly after removal. It was found that the presence of bile could be traced in most instances to one of two causes. Either the tip of the tube had slipped into the duodenum, or bile had been regurgitated as a result of nausea and retching. We, therefore, discarded all those specimens which contained bile, although in some instances this may have been the result of normal regurgitation from the duodenum. However, it seemed that this rule would result in more accurate data.

All specimens were analyzed in the usual manner for free and total acidity, using Topffer's reagent and 1 per cent alcoholic phenolphthalein respectively. One observer (P. H. W.) performed all the titrations with tenth normal sodium hydroxide, and the results are expressed in the number of c.c. of a decinormal solution of sodium hydroxide required to neutralize 100 c.c. of gastric juice. (Clinical units.)

DATA AND DISCUSSION

Chart 1 shows the results of 30 determinations made when the patients were taking milk and cream, and 46 determinations on patients taking the "first day Sippy." The free acidity was somewhat higher with only

milk and cream (an average of two clinical units) than if the alkaline powders were added. A comparison of the curves obtained on patients taking only milk and cream with those obtained when patients were taking the "seventh day" and "fourth week" management (charts 2 and 3) shows

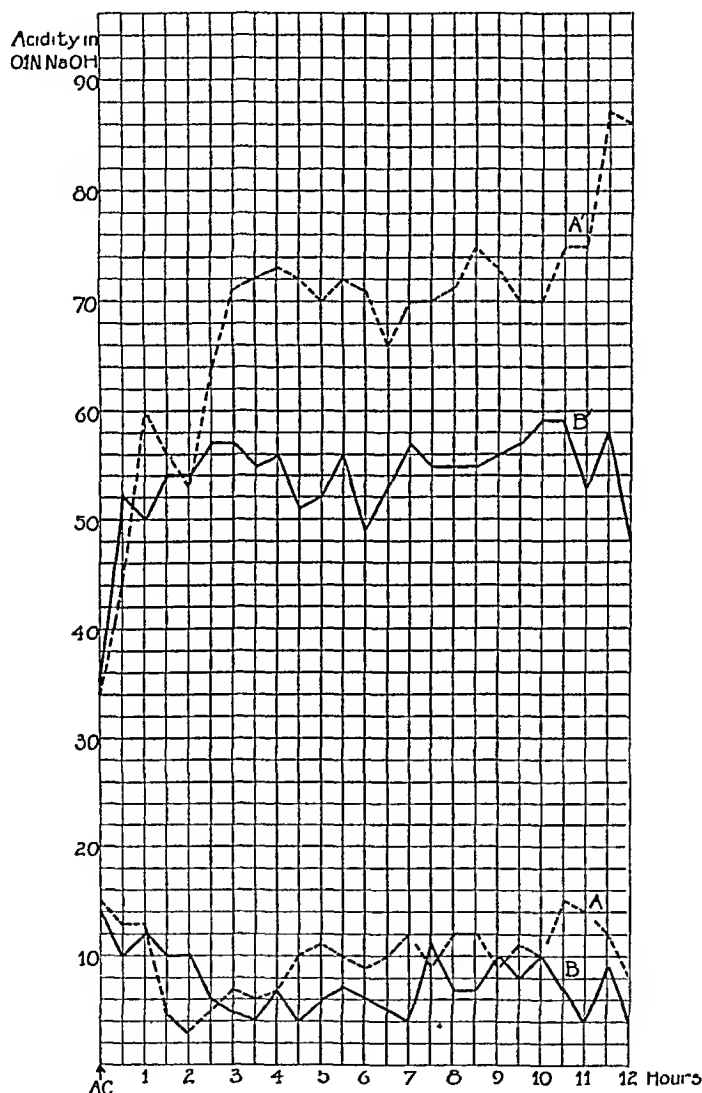


CHART 1 Free and total acidity curves on 30 patients who were given hourly feedings of milk and cream (A and A') and on 46 patients who, in addition to the milk and cream, were given calcium carbonate 0.6 gm and sodium bicarbonate 2.0 gm and on the half-hour, the first day Sippy regimen (B and B')

that, at no time, did the giving of alkali increase the amount of free acid present

Chart 2 compares the results of the "first" and the "seventh day" diets. The free acidity in the latter was distinctly lower. It was zero part

of the time and only on a few occasions rose above four. This drop in the free acidity was probably due to the longer period of rest (often two weeks), the combining power of the food for acid, and the ease with which these soft

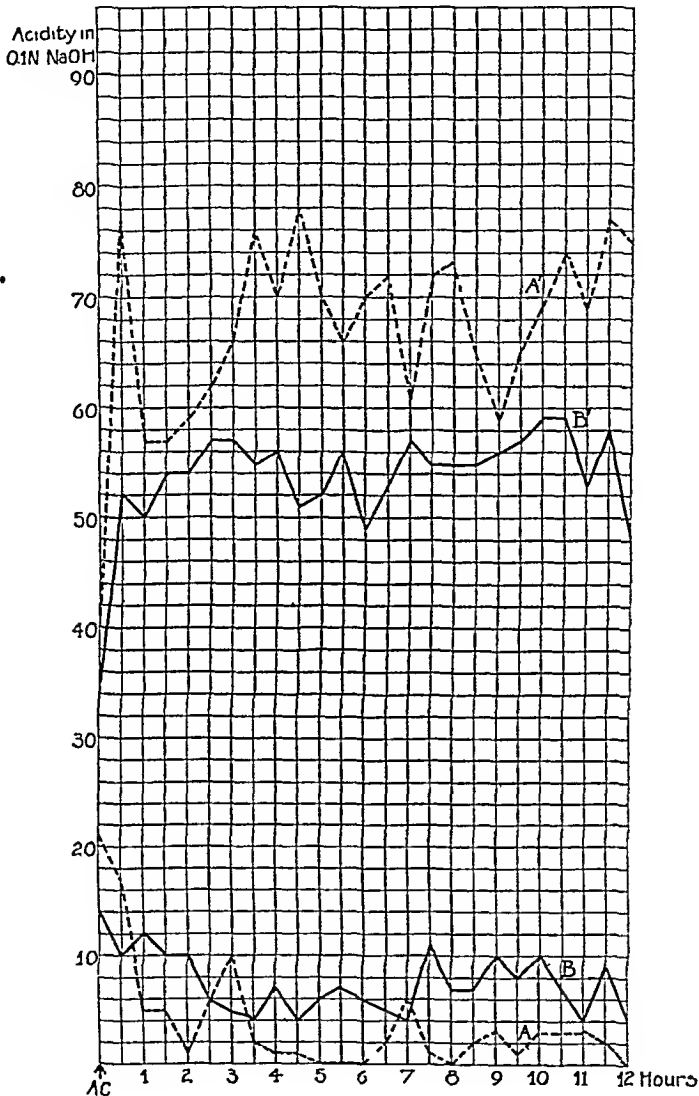


CHART 2 Free and total acidity curves of 46 patients who were given the first day Sippy regimen (B and B') and 14 patients taking the seventh day Sippy regimen (A and A')

foods passed from the stomach. That an increase in the amount of acid was present may be seen by the total acid curve.

Chart 3 shows that the average free acidity was distinctly higher in the "fourth week" than on the "seventh day," and was somewhat higher than on the "first day Sippy." This increase in the free acidity accompanies greater activity on the part of the patient as well as the wider variety of

foods Because Sippy recognized this fact, he included the "fourth week" in his regimen, thus enabling him to overcome any higher values of acidity by changing the size of the powders The curve for the total acidity was much the same as on the "seventh day"

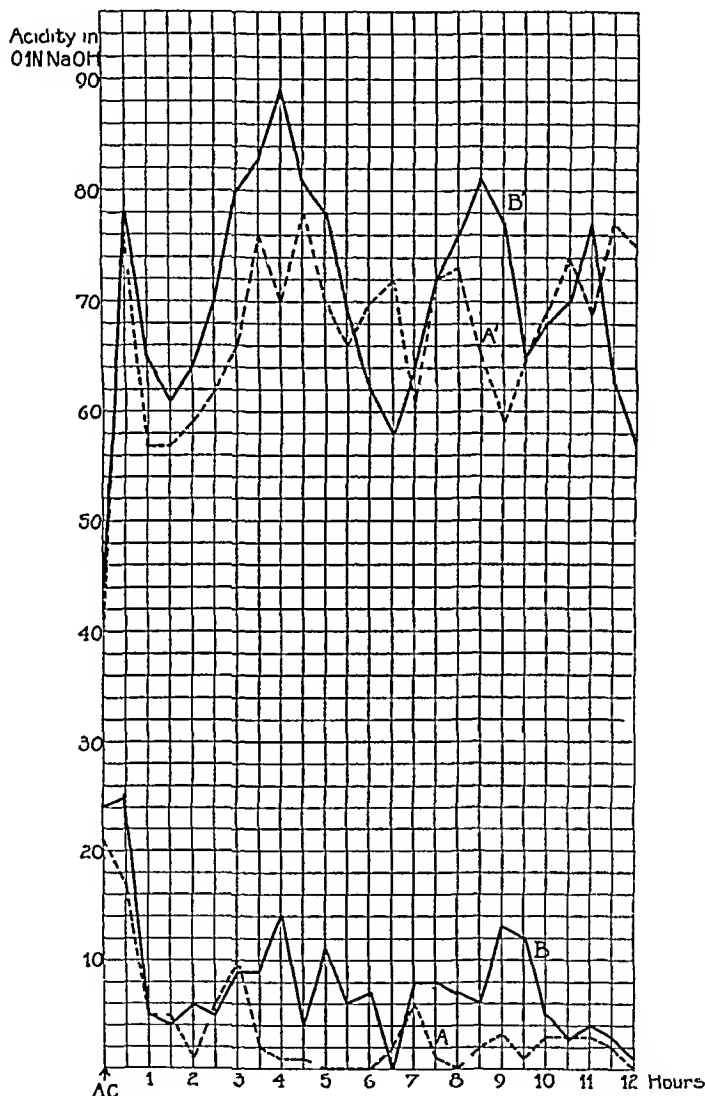


CHART 3 Free and total acidity curves on 14 patients on the seventh day Sippy regimen (A and A') and 14 patients on the fourth week Sippy regimen (B and B')

Although control of the free acidity is presumably the important factor of the Sippy treatment, the values for the total acidity have been given on the charts. It is seen that the total acidity was the same in all instances except on the first day that alkaline powders were instituted, where the readings average 14 points lower. This may be seen on chart 1. Because of the relatively large amount of data accumulated, we thought it might be

interesting to calculate the effectiveness of the alkalis, using the total acid determination as a basis without considering the free acid. Thus, if we assume that the stomach secretes approximately 1500 c c of juice daily, or about 50 c c per hour, with a total acid value of 150 clinical units, the hourly secretion of hydrochloric acid will be 7.5 milli-equivalents (274 mg). The amount of sodium bicarbonate required to neutralize this amount of acid can be calculated as 630 mg. Actually the average value for total acid was lower by only 14 clinical units on the days of alkali administration than on control days with only milk and cream (Chart 1). This is a difference of 0.7 meq of acid hourly, while the alkali given amounted to 35.0 meq hourly. In other words, on the average, 50 times more alkali was given than was actually used for purposes of neutralization. However, it may be maintained that the hourly secretion rate is higher where ulcers are found. Assuming, then, a secreting rate of 100 c c per hour, we still find that 25 times more alkali was used than should have been necessary in the neutralization process. These average values, however, are perhaps misleading since a wide variation in effectiveness was encountered as may be noted from table 1. But it seems clear that the majority of patients require amounts of alkali greatly in excess of that which is needed to neutralize the maximum amount of acid, which we believe the stomach to be capable of secreting.

There are two explanations for the fact that the amount of alkali required is much larger than the theoretical value calculated from the estimated rate of gastric secretion. The alkali may induce a more rapid emptying of the stomach, or may stimulate gastric secretion. Both possibilities should be considered. It seems probable, however, that rapid emptying is the more important.

Since these charts did not show the effect of the treatment on individual cases, table 1 has been included. The patients were divided into four groups as follows. Group 1 shows the percentage of cases which were completely controlled, i.e., those exhibiting no free acid during the day of the test, Group 2 includes those patients whose acidity never went above 10, Group 3 includes those patients whose acidity occasionally went above 10, but never

TABLE I

Showing the Relative Percentages of Effectiveness of Milk and Cream and Various Stages of the Sippy Treatment on the Gastric Acidity

Group	Gastric Acidity in Terms of 0.1N NaOH	Per cent of Cases			
		Milk and Cream	First Day Sippy	Seventh Day Sippy	Fourth Week Sippy
1	No free acidity	7%	10%	14%	7.1%
2	No reading over 10	10%	13%	7%	7.1%
3	No reading over 20	16.6%	13%	35.7%	28.5%
4	One or more readings over 20	66.6%	63%	42.8%	57%

over 20, and, Group 4, those patients whose acidity was above 20 on at least one occasion. The table shows again that the best results were obtained on the "seventh day" and that in general, the results on the "fourth week" were similar to the "first day."

We have classified as adequately controlled (1) those showing no free acid, (2) those showing free acid (below 20 clinical units) on not more than three occasions, provided the acidity did not occur in consecutive specimens, and (3) those having readings above 20 on one occasion but completely controlled the rest of the time. On this basis, 54 per cent were adequately controlled on the "first day," 71 per cent on the "seventh day," and 57 per cent on the "fourth week Sippy." These figures indicate that only a little more than one-half of the patients were controlled without any attempt being made to vary the size of the powders. Sippy recognized the importance of individual variations, for he states, "Control of the free hydrochloric acid should be maintained from the beginning," and he adds later, "It should be understood, however, that the presence of free hydrochloric acid now and then for a few minutes each day may not seriously interfere with the healing of the ulcer."

Since it would be of value to know before treatment is instituted in which patients adequate control can be expected, we tried to correlate the results of treatment with the fractional gastric analyses that were performed in all cases before the patient was placed on treatment. Fifty cc of 8 per cent alcohol were used as a test meal. The number of patients that were adequately controlled was then compared with the results of the gastric analyses, using the highest reading of the free acidity as the index. Adequate control occurred in all patients whose free acidity did not go above 20 at the time of the analysis. For those patients in whom the acid went above 20, the number of those adequately controlled fell markedly. It seemed to make little difference how far above 20 the acidity went. Fifty per cent of those patients whose acidity fell between 20 to 40 were controlled, 64 per cent of those between 40 to 60, and 65 per cent of those above 60. Since the number of cases in which the acidity remains below 20 is small, gastric analyses are of little aid in determining which patients will be controlled by the regimen. An attempt to use the average for all determinations of the gastric analysis as an index was found to be even less satisfactory.

We are unable to say what effect the continuous presence of the tube in the stomach may have had on these values. It is probable that the annoyance and discomfort, which the presence of the tube entails, would decrease the gastric response.

The treatment, as used, abolished all symptoms in all patients, usually by the second day and without exception by the fourth day. There appeared to be little difference in the clinical response of those patients in whom the acid was satisfactorily controlled as compared with those in whom adequate neutralization was not obtained. The present series is too small to permit an accurate estimate of the relationship between symptomatic relief

and effectiveness of acid neutralization, and we do not wish to enter upon that controversy at present. We can only say that in the present series no such relationship was apparent. The slight difference between the acid values on milk and cream alone and those when alkalis were added is significant in this connection, our data indicate that the addition of alkali to hourly milk and cream feedings produces but little decrease in free acid. This phase of the problem should be studied further.

We feel that the results here presented are helpful in understanding what is accomplished by alkali therapy in ulcer. Because the control was not absolute in all cases, we should not question the large amount of clinical experience which has demonstrated the effectiveness of alkali therapy in peptic ulcer.³ It does suggest that a more efficient regimen might be developed, and emphasizes that each patient should be considered individually.

SUMMARY

1 Forty-six patients with duodenal ulcer received the routine Sippy treatment. Specimens of gastric contents were removed every half hour from 7 a m to 7 p m and the free and total acid determined when only milk and cream were given and on days corresponding to the "first day," "seventh day," and "fourth week" procedures of Sippy.

2 The treatment given abolished symptoms in all cases.

3 The free acidity was adequately controlled in more than one-half of the patients, even though no variations were made in the amount of alkali given.

4 The data show that if the free acidity does not rise above 20 after an alcohol test meal, the patient will obtain adequate control by this treatment. There seem to be no criteria to determine which patients will be controlled in the larger group whose free acidity goes above 20 following an alcohol test meal.

5 Calculations suggest that 25 to 50 times more alkali was given than should be necessary theoretically.

6 If a routine treatment is used, one can be assured of complete neutralization only if frequent aspirations are performed.

THE VALUE OF A MIXTURE OF POWDERED MILK AND ALKALI FOR NEUTRALIZING THE GASTRIC ACIDITY OF PATIENTS WITH PEPTIC ULCER *

By PAUL H. WOSIKA, M D , *Chicago, Illinois*, and EDWARD S. EMERY, JR., M D , *Boston, Massachusetts*

SINCE Sippy introduced his method of treating patients affected with peptic ulcer, there has been no unanimity of opinion among the medical profession concerning its therapeutic value. Those who oppose the treatment do so largely on the ground that large amounts of alkali are contraindicated, and that the results do not justify the time and trouble which the treatment entails. Its enthusiastic advocates maintain that complete neutralization of the gastric contents can be obtained if the treatment is carried out properly and that better results will follow this therapy. They argue that the poor results claimed for the therapy by others follow a failure to administer the treatment properly.

Recent studies of the disease teach us that the important essentials of treatment consist of control of the gastric acidity and of debilitating influences such as fatigue, emotion and infection. The best form of treatment will control these factors, and the Sippy therapy is suited best for neutralization of the gastric contents. Unfortunately the frequent feedings, which are the only sure way to obtain neutralization, constitute in the opinion of all a serious objection to this mode of treatment. Patients dislike the bother of taking something every half hour and in many instances will not follow the regimen carefully or thoroughly enough to accomplish its purpose. To meet this objection many physicians are prone to introduce so-called modifications which so alter the efficacy of the treatment as to do away with whatever advantages it may possess over other therapeutic procedures. These modifications appear justified because frequently they will relieve symptoms as quickly and completely as Sippy's published regimen. But early relief from pain is a disadvantage, if it misleads the patient and physician into a false idea that healing is taking place with the result that other important aspects of treatment are ignored. Hence one must condemn modifications whose sole object is to provide relief. But a modification that will retain the value of the Sippy treatment and at the same time eliminate many feedings will be a distinct advantage. We are therefore suggesting a modification which seems to fulfill these requirements.

In the spring of 1933 one of our patients inquired about the justification of adding the prescribed Sippy powders to his milk. He believed that this procedure gave him a longer period of relief and that he did not require

* Received for publication October 18, 1935

From the Medical Clinic of the Peter Bent Brigham Hospital. The expenses of this study were defrayed by the Upjohn Company.

medication every half hour. Therefore, we decided to investigate the effect of powdered milk on the gastric juice, for, if this could be substituted for whole milk and cream, it would be a simple way for a patient to take an alkalinized milk product. This paper compares the effect on the gastric acidity of an alkalinized powdered milk with the effect of a routine Sippy regimen.

METHOD OF STUDY AND DATA

We have already prepared a detailed account of the method of investigation¹. To summarize it, we studied 46 patients with duodenal ulcer. A stomach tube was passed in the morning and allowed to remain in the stomach for 12 hours while 5 c c of gastric contents were withdrawn every half hour. One observer (P H W) performed all titrations for the free and total acidity in the usual manner, using Topffer's and 1 per cent phenolphthalein solutions as indicators. The patients were studied at various stages of the routine Sippy regimen—namely, the first day, seventh day, and fourth week. We also investigated the effect of milk and cream without powders. Next we determined the effect on the same patients of a commercial preparation of powdered milk. For this purpose we used 12.5 gm of "Klim" or "Parlac" mixed with 90 c c of water. According to the formula given for these products, patients received from 12.5 gm of the product approximately 4.75 gm of carbohydrate, 3.33 gm of protein, 3.5 gm of fat, with a total caloric value of 64. Ninety c c of the mixture of milk and cream ordinarily used in the Sippy treatment contain 4.27 gm of carbohydrate, 2.6 gm of protein and 10.12 gm of fat, with a total caloric value of 118.56. The commercial preparation afforded 22.1 per cent more protein, 65.5 per cent less fat, and about half as many calories.

The effect on the gastric acidity of using 90 c c of whole milk and cream is compared in chart 1 with the effect of 12.5 gm of powdered milk. The chart shows that the results are quite similar with both preparations, although with the powdered milk, the free acidity drops toward the end of the day to a level slightly below that obtained with whole milk and cream. The total acidity was much the same in both instances. These figures convinced us that 12.5 gm of powdered milk controlled the gastric acidity as successfully as 90 c c of milk and cream.

The next step was to compare the effect of an alkalinized powdered milk with the usual Sippy treatment. Therefore, we mixed 0.6 gm of calcium carbonate and 2 gm of sodium bicarbonate (the dose with which Sippy initiated treatment) with the 12.5 gm of powdered milk, and the entire mixture was given to the patient in 90 c c of water. This was repeated every hour. This method, if successful, would decrease the number of medications from approximately 29 to 14.

The results of this procedure, as compared to those with the routine Sippy, are shown in charts 2, 3, and 4. Chart 2 shows the average of 46 determinations on the first day Sippy. Water was allowed in small quanti-

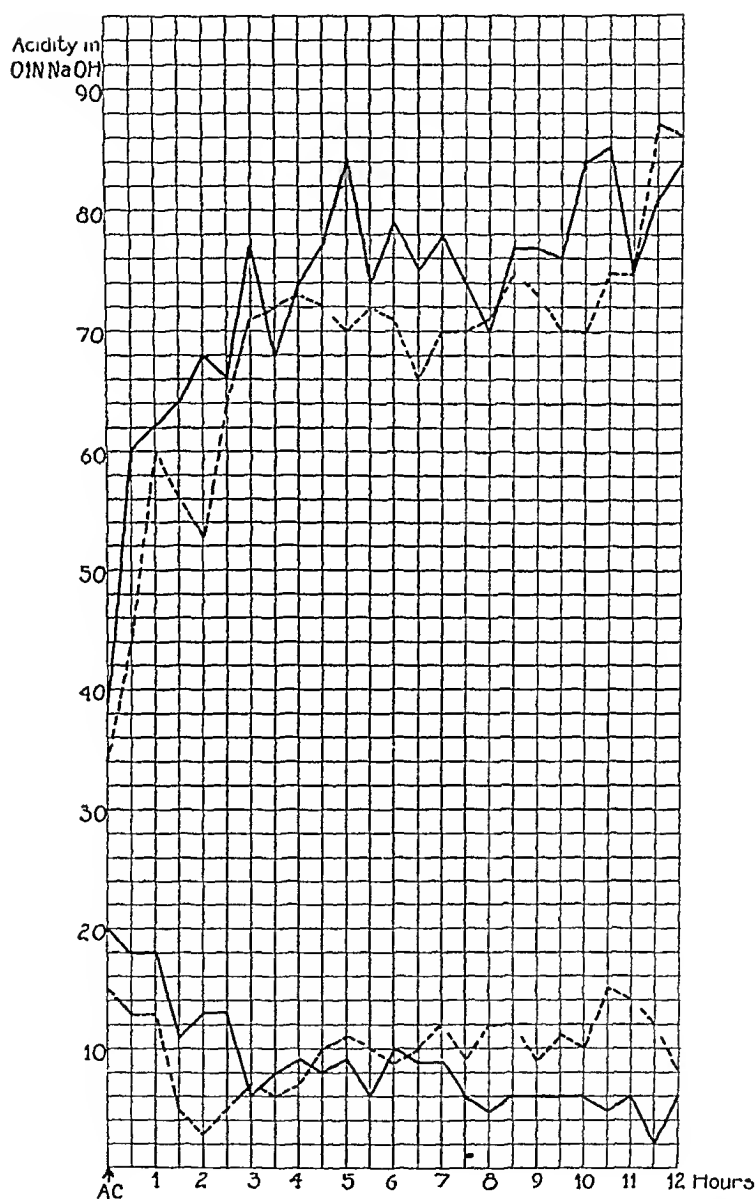


CHART 1 Shows the average free and total acid curves of plain powdered milk (12.5 gm) (solid line) on 28 patients, compared with milk and cream (90 cc) (broken line) on 30 patients

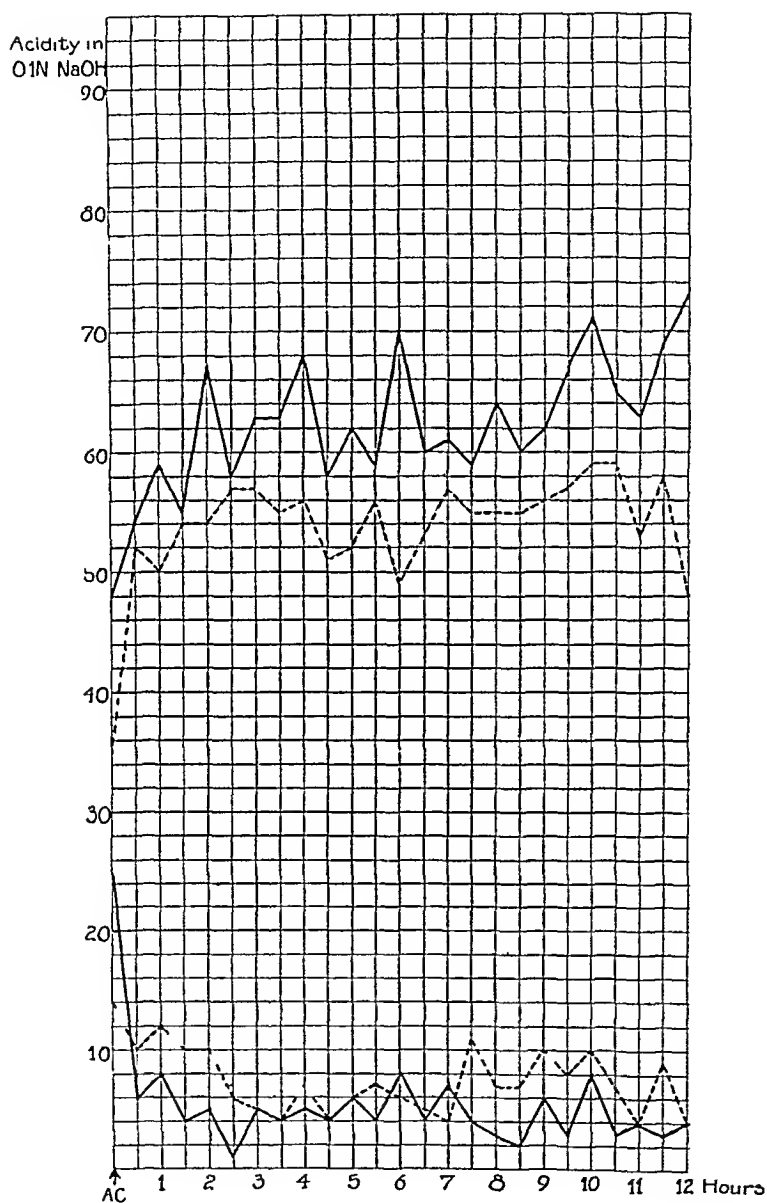


CHART 2 Shows the average free and total acid curves of alkalinized powdered milk (125 gm plus one Sippy powder) (solid line) on 45 patients compared with the routine first day Sippy (broken line) on 46 patients

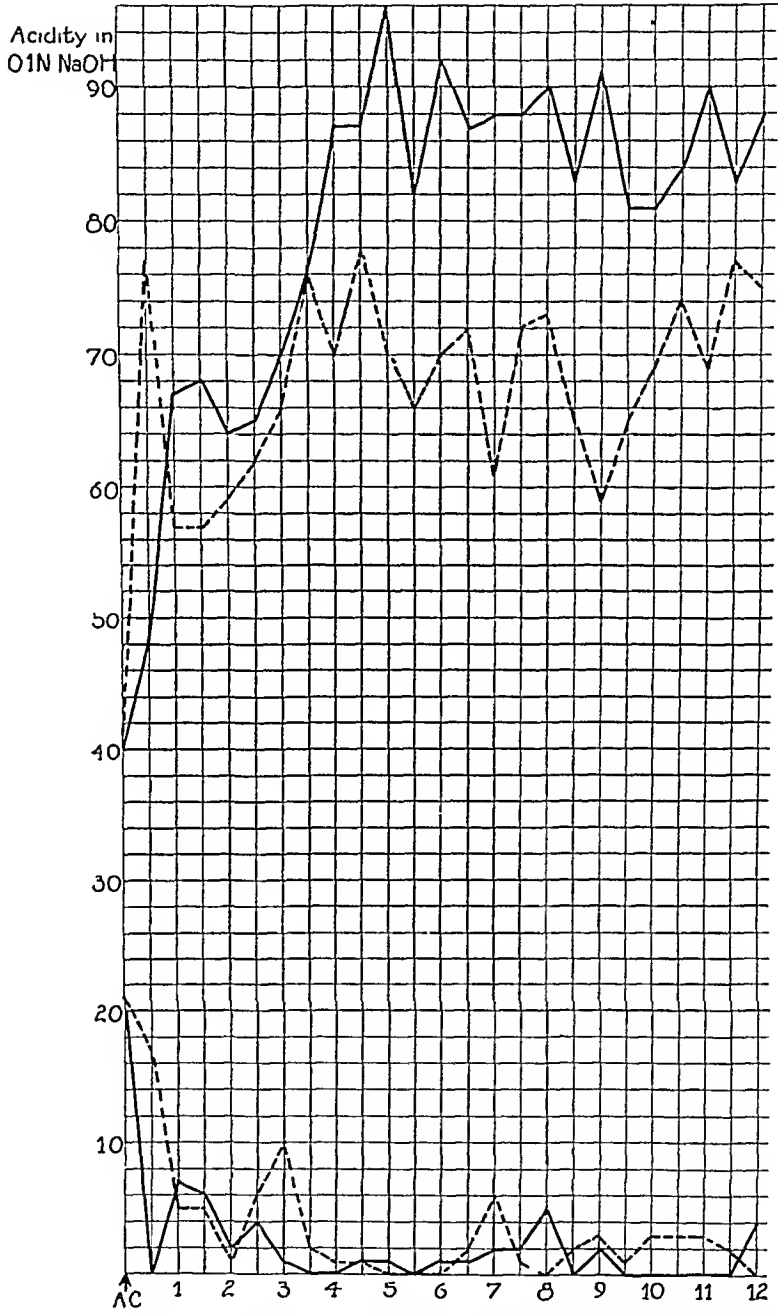


CHART 3 Shows the average free and total acid curves on the routine seventh day Sippy (broken line) on 14 patients, compared to hourly alkalized powdered milk and 6 small feedings (solid line) on 17 patients

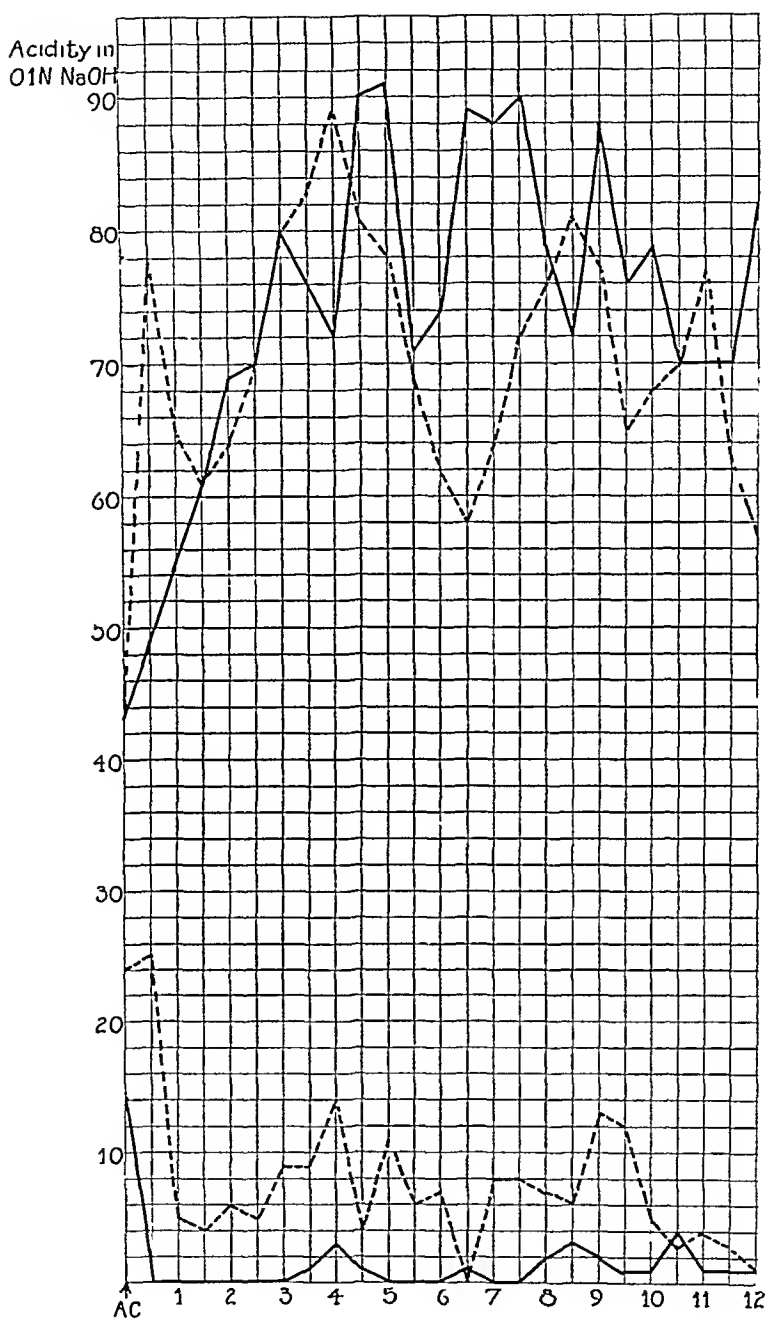


CHART 4 Shows the average free and total acid curves on the routine fourth week Sippy (broken line) on 14 patients, compared with the same feedings but using alkalinized powdered milk (solid line) on 17 patients

ties, usually in the form of cracked ice in addition to the milk and alkalis. The free acidity remained low under both methods. The curve for total acidity was the same whether whole milk and cream or powdered milk was used. It is interesting to note that the total acidity was less when no alkali was given (compare with chart 1).

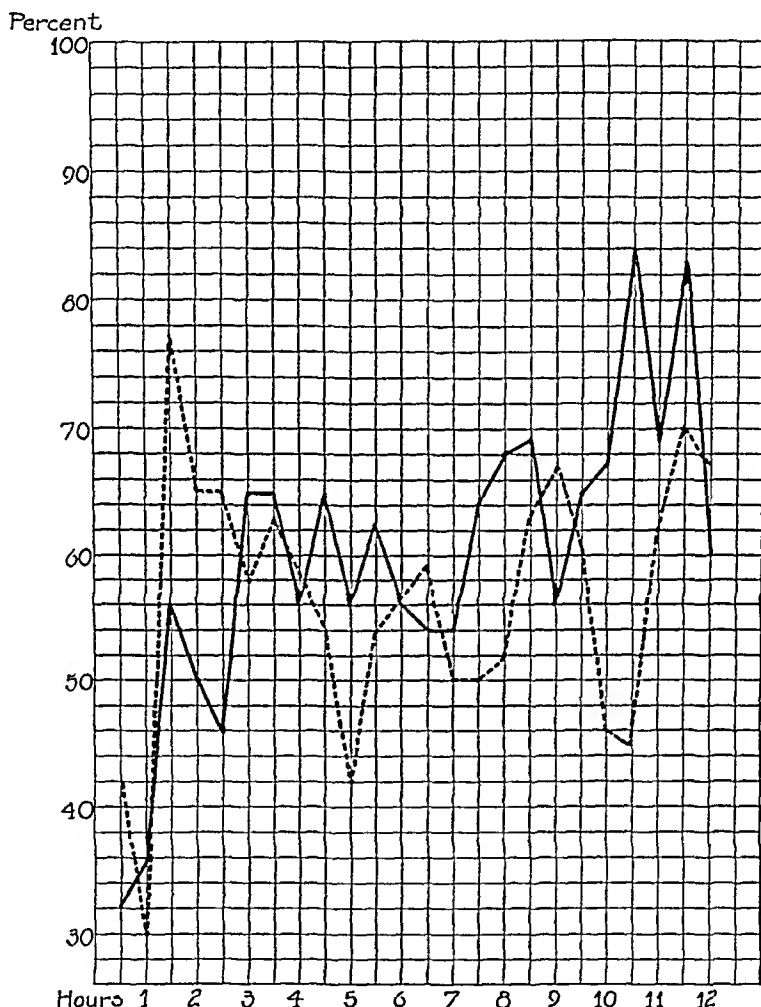


CHART 5 Shows the percentage of patients who had no free acid using powdered milk (solid line) on 28 patients and milk and cream (broken line) on 30 patients for half hour periods in 12 hours

Chart 3 shows the effect of both treatments on the seventh day, at which time the patients were receiving six small feedings in addition to the milk and alkalis. Observations were made on 14 patients who were receiving whole milk and cream with powders on the half hour, and 17 patients who were taking the alkalinized milk powder. The curves for both free and total acidity are virtually identical. The total acidity has again risen to the same level that existed before alkalis were started.

The results obtained on patients in the fourth week of treatment are shown in chart 4. The patients were receiving the same kind of treatment as on the seventh day, with the exception that the six feedings had been changed to three meals. They were encouraged to be up and around the wards in order to approximate as closely as possible the conditions under which they would live after leaving the hospital. The chart shows that

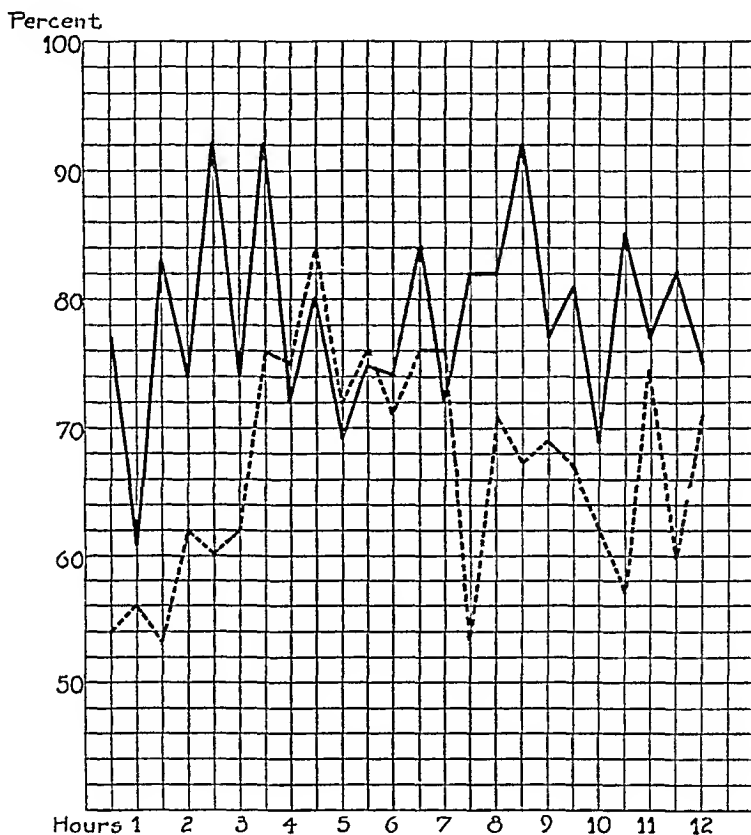


CHART 6 Shows the percentage of patients who had no free acid when alkalinized powdered milk (solid line) was used on 45 cases and the routine first day Sippy (broken line) was used on 46 patients

hourly feedings of alkalinized milk powder controlled the gastric acidity about as well as whole milk and cream with powders given on the half hour.

Although these charts show the average effect on all the patients by the milk and powders and alkalinized powdered milk, they give no clue as to the effect on the individual patient. Therefore, charts 5, 6, 7, and 8 are included to show the percentage of patients who showed no free acid for each half hour throughout the day. It is seen that the alkalinized powdered milk reduced the gastric acidity to zero in a much higher percentage of instances than the routine Sippy treatment.

In our previous report we discussed the efficacy of the routine Sippy procedure in producing adequate control of the gastric acidity. Included as being adequately controlled were (1) Patients whose gastric contents never showed free acid during the 12 hours of observation (2) Patients in whom the gastric contents showed free acidity of not more than 20 and was not found on more than three occasions provided this finding did not occur in consecutive specimens (3) Patients in whom the gastric contents

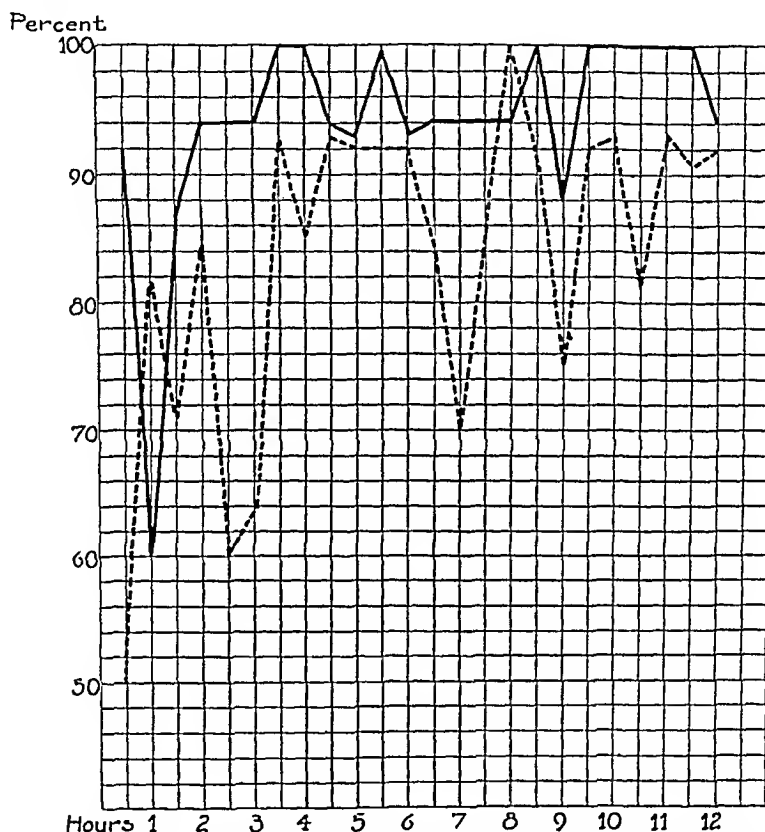


CHART 7 Shows the percentage of patients who had no free acid using alkalinized powdered milk plus 6 additional feedings (solid line) on 17 patients and the routine seventh Sippy (broken line) on 14 patients

showed a reading above 20 on one occasion, but were completely controlled the rest of the time

This classification gives us a means of comparing the efficacy of the routine Sippy treatment with the alkalinized powdered milk. Table 1 shows that 90 c c of milk and cream and powdered milk without alkali were equally efficacious. Milk and cream adequately controlled 47 per cent of the patients, compared to 50 per cent on powdered milk. However, when alkalies were added, the alkalinized powdered milk gave much more satisfactory results. On the first day, 75 per cent were adequately controlled with

alkalinized powdered milk to 54 per cent by the routine Sippy. On the seventh day, the figures were 94.1 per cent by alkalinized powdered milk to 71 per cent by the routine Sippy, and on the fourth week, 94.1 per cent to 57 per cent.

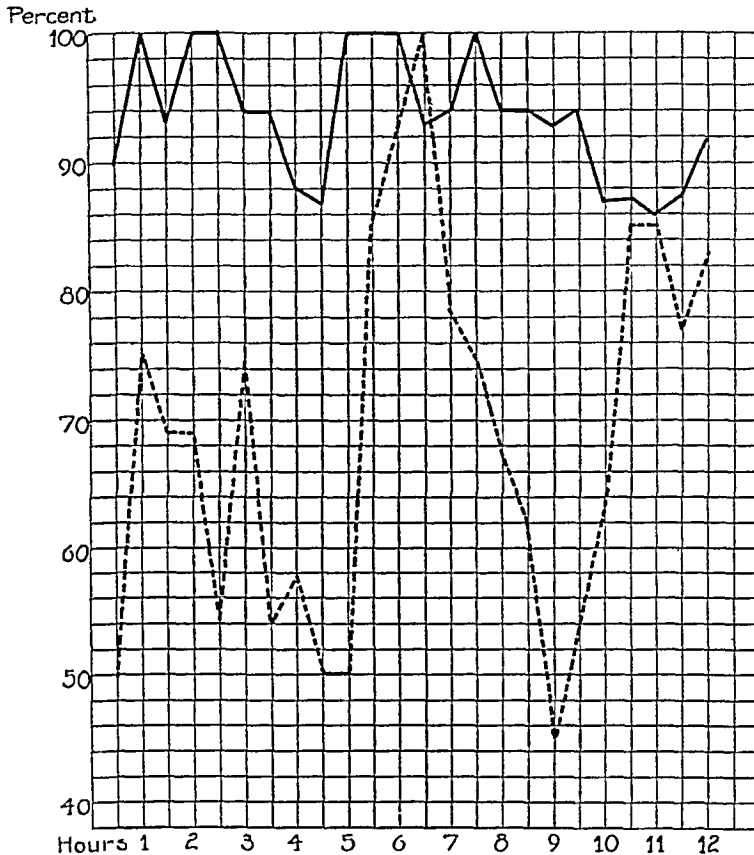


CHART 8 Shows the percentage of patients who had no free acid using alkalinized powdered milk and three meals (solid line) on 17 patients and the routine fourth week Sippy (broken line) on 14 patients

DISCUSSION

These results were more satisfactory than we had expected. The most we had hoped for was a method which would simplify the treatment of the patient without sacrificing its efficiency. According to the present observations, the method is even more efficient as a means of neutralization than the usual procedure.

We have no data that explain the greater efficiency which the alkalinized powdered milk seems to possess. A greater dilution would lower the titratable acidity, but even less fluid was given by this method than the ordinary Sippy. It is hard to estimate what effect a difference in flavor might have. Most of the patients enjoyed the whole milk and cream better than the powdered milk. This became more pronounced when the patients

TABLE I

Showing the comparative results of milk and cream and routine Sippy procedures with powdered milk with similar feedings expressed in per cent Although the number of medications is one-half when powdered milk is used, the percentage of adequately controlled patients is seen to be higher

Group	Classification of Patients by Amounts of Free Acid Present	Procedure with Milk and Cream	Procedure with Powdered Milk
		Percentage control of 30 patients using milk and cream without alkalis	Percentage control of 28 patients using powdered milk without alkalis
1	No free acid	7	10 7
2	No reading over 10	10	7 1
3	No reading over 20	16 6	21 4
4	One reading over 20	66 6	60 7
	Adequate control	47	50
		Percentage control of 46 patients using the first day Sippy regimen	Percentage control of 44 patients using alkalized powdered milk once an hour
1	No free acid	10	34
2	No reading over 10	13	4 5
3	No reading over 20	13	22 7
4	One reading over 20	63	38 6
	Adequate control	54	75
		Percentage control of 14 patients using the routine seventh day Sippy	Percentage control of 17 patients using alkalized powdered milk with six additional feedings
1	No free acid	14	47
2	No reading over 10	7	11 7
3	No reading over 20	35 7	17 6
4	One reading over 20	42 8	23 5
	Adequate control	71	94 1
		Percentage control of 14 patients using the routine fourth week Sippy	Percentage control of 17 patients using alkalized powdered milk with three meals
1	No free acid	7 1	47
2	No reading over 10	7 1	23 5
3	No reading over 20	28 5	5 9
4	One reading over 20	57	23 5
	Adequate control	57	94 1

knew that it was powdered milk. However, it does have a flatter taste. A smaller "appetite secretion" might, therefore, result. On the other hand, the addition of three meals a day, which the patient received on the "fourth week" diet, not only failed to increase the amount of free acidity, but the patients were controlled more completely. The failure of the usual foods

to stimulate a greater secretion of acid argues somewhat against the idea that the "appetite secretion" made much difference. The greater amount of protein in the powdered milk should decrease the amount of free acid by increasing the amount of neutralization. As already pointed out, the powdered milk provided about one-fifth more protein than the milk and cream. It was also noted that the milk curds obtained in the samples were smaller with the powdered milk than with the whole milk. This suggests, of course, that the protein in the powdered milk could neutralize the acid more effectively.

Another observation makes us feel that the increased amount of protein is an important factor in the greater degree of neutralization. If we increased the amount of milk powder to patients whose acidity was not entirely neutralized by the 12.5 gm. dose, there resulted an increased degree of neutralization comparable to the greater effectiveness which seemed to exist with the alkalinized powdered milk over the ordinary Sippy. This difference could not be explained by the difference in "appetite secretion." Therefore, we feel that even though a difference in flavor may play some rôle, the alkalinized milk powder is more effective as a neutralizing agent.

This method of treatment has certain practical advantages. Mixing the dried milk with the alkaline powders overcomes the necessity of a patient carrying both fresh milk and powders. It also decreases the number of medications by one half, which is a distinct advantage to the patient who works. Finally, it costs somewhat less than if equal parts of whole milk and 20 per cent cream are taken, provided a non-advertised brand of powdered milk is purchased.

Among its disadvantages may be listed the taste, which is not pleasant to one unaccustomed to it. However, the taste is largely a matter of habit, and patients will overcome this objection in a short time. Moreover, a failure to stimulate secretion by the absence of flavor really is an advantage. The fewer number of calories which the powdered milk supplies can be taken care of easily by increasing the other simple foods allowed in the diet. Its greatest disadvantage is the difficulty of mixing the powder with the water. It tends to adhere to the glass and requires much stirring to obtain a smooth mixture. But we hope to circumvent this disadvantage by having the mixture made into tablets.

We do not wish to suggest this treatment as a substitute for the Sippy regimen, the object of which is to neutralize adequately the gastric acidity of every patient with ulcer. A physician can be sure of adequate neutralization only if he performs frequent aspirations and increases the amount of alkali to those patients who require it. No method of therapy which utilizes a fixed amount of milk and cream and alkali can be expected to neutralize completely the gastric juice of all patients. We feel that this method is a distinct advantage for those physicians who utilize the routine Sippy treatment, but for one reason or another do not attempt to secure complete neutralization.

More recent studies demonstrate that complete neutralization is not an essential requirement for healing. Many ulcers heal spontaneously in the normal course of events without any treatment. Those experiments which incriminate the acid as a cause of ulcers depend upon the prevention of all neutralization by duodenal regurgitation, which suggests that the development of an ulcer may follow from an interference with this normal means for regulating the acidity. The use of an alkalinized milk powder at hourly intervals should neutralize the gastric acidity as effectively as duodenal regurgitation. Continued use of such a regimen should, therefore, regulate the stomach contents in such a way as to prevent the development of unusual degrees of acidity. The change in the incidence of feeding from half hourly to hourly intervals will permit a much larger group of individuals to carry out this simplified regimen.

SUMMARY

It has been found that 12.5 gm. of a preparation of powdered milk mixed with the usual Sippy powder containing 0.6 gm. of calcium carbonate and 2.0 gm. of sodium bicarbonate, and given at intervals of one hour, are somewhat more effective in neutralizing the gastric acidity than 90 cc. of milk and cream and the same powder given in the usual way advised by Sippy.

REFERENCE

1. WOSIKA, P. H., and LEMERY, E. S., JR. The effectiveness of the Sippy regimen in neutralizing the gastric juice of patients if the amount of alkali is not varied. (See p. 1070 in this issue of the ANNALS.)

STUDIES IN HYPERTENSION; A PROPOSED CLASSIFICATION OF HYPERTENSION BASED UPON THE NITROGEN DISTRIBUTION OF THE SERUM PROTEINS *

By HENRY A RAISKY, F A C P, ADOLPH BERNHARD, and GEORGE L ROHDENBURG, *New York, N Y*

IN a previous publication¹ we reported that experimental hypertension in rabbits produced by the injection of a mono-amino acid (aspartic acid) is associated with definite alterations in the nitrogen distribution of the serum proteins. These changes are an increase in the mono-amino nitrogen and a decrease in the basic amino nitrogen with a resultant change in the ratio between these two fractions (referred to as the M/B ratio). We have noted in further studies similar changes in the nitrogen distribution of the serum proteins in hypertension in man. Since these changes offer a basis for the classification of hypertension, the results of this investigation are reported in this paper.

Methods The blood pressure readings were obtained either with the sphygmotonomograph or a mercury manometer. The procedure for taking the blood specimens, the separation of the serum proteins and the technical methods for the analysis of the blood protein fractions have been described in detail elsewhere². The amide and humin nitrogen were both removed before the other fractions were determined, consequently, they are of no significance in the present discussion.

EXPERIMENTAL RESULTS

Normal Values Table 1 shows the nitrogen distribution of the serum proteins in a group of 20 normal adults, most of whom were hospital interns between 21 and 30 years of age, the average being 26 years. The systolic blood pressure varied between 104 and 135, the average pressure being 117. The diastolic pressure ranged between 50 and 95, with an average of 76. The pulse pressure varied between 28 and 56, with an average of 41. All of the group were free from renal, cardiac, and metabolic disturbances.

In this group the total nitrogen varied between 420 and 700, with an average of 532 mg per 100 c c blood. The basic amino nitrogen varied between 100 and 190, with an average of 140 mg. In only one instance was it as low as 100 mg, while in 15 cases it ranged between 110 and 150 mg. This fraction represents 23 to 40 per cent of the total nitrogen after hydrolysis, with an average of 28 per cent. The lowest mono-amino nitrogen value was 190 mg, the highest 330 mg, and the average 269 mg. It

* Received for publication October 12, 1935.

From the Achelis Laboratory of the Lenox Hill Hospital under a grant from the W. C. Durant Fund.

TABLE I
Nitrogen Distribution of the Serum Proteins in Normal Adults

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen * after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm Hg	mg per 100 c c				mg per 100 c c			
115	26	130/80	570	510	120	23	380	220	43	1.8
116	24	120/80	700	680	190	28	490	310	46	1.6
117	28	118/70	600	550	150	27	390	330	60	2.2
118	24	105/70	600	570	130	23	430	260	45	2.0
119	28	135/85	630	600	180	30	420	230	38	1.3
120	26	118/70	530	450	130	29	310	310	69	2.3
121	25	115/80	530	480	150	31	320	300	62	2.0
122	32	114/70	600	580	190	33	390	310	53	1.6
123	29	104/70	560	470	190	40	280	190	40	1.0
3	28	130/78	530	510	130	25	370	250	48	1.9
4	21	106/76	480	470	130	27	320	240	51	1.8
8	27	120/70	550	540	140	26	400	300	55	2.1
10	27	116/63	520	500	140	28	360	280	56	2.0
18	25	106/50	510	490	130	27	360	290	59	2.2
27	28	120/80	470	450	130	29	320	280	62	2.1
28	31	112/80	500	480	120	25	360	280	58	2.3
79	25	130/95	450	430	130	30	390	280	65	2.1
80	24	118/90	420	400	100	25	300	220	55	2.2
81	28	126/80	460	430	110	25	320	250	58	2.2
83	25	110/82	430	400	120	30	270	260	65	2.1
High	32	S135 D95	700	680	190	40	490	330	69	2.3
Low	21	S104 D50	420	400	100	23	270	190	40	1.0
Average	26	S117 D76	532	499	140	28	359	269	54	1.9

Pulse Pressure High 56, Low 28, Average 41

* After the removal of humin and amide nitrogen

The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen

was between 200 and 300 mg in 13 cases (65 per cent) and in 6 cases (30 per cent) between 300 and 330. The mono-amino nitrogen expressed as percentage of the total nitrogen after hydrolysis varied between 40 and 69, with an average of 54. The M/B ratio varied between 1.0 and 2.3, with an average of 1.9. The ratio in one case was 1.0, in 6 cases (30 per cent) between 1.1 and 1.9, and in 13 cases (65 per cent) between 2.0 and 2.3.

Control Cases without Hypertension Table 2 records the nitrogen distribution in 11 individuals who, while not normal, suffered from conditions in which hypertension was not a factor, four were cases of cardiac disease, three of diabetes and one each of tetany, carcinoma of the rectum, and hemiplegia. The ages of this group varied between 29 and 81 years and the blood pressure between 105 systolic and 70 diastolic and 140 systolic and 70 diastolic. The basic amino nitrogen was slightly lower, while the mono-amino nitrogen values approximated those of the normal group. The

TABLE II

Nitrogen Distribution of Serum Proteins in Miscellaneous Disease Conditions without Hypertension

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm Hg	mg per 100 c c				mg per 100 c c			
9	61	130/90	430	400	100	25	300	290	72	2.9 Myocarditis
44	74	140/70	500	480	120	25	360	290	60	2.4
113	38	112/74	580	500	100	20	400	320	64	3.2
15	50	140/90	530	510	120	23	390	290	57	2.4 Sinus arrhythmia
64	71	120/70	530	520	120	23	400	300	57	2.5 Diabetes
76	71	130/80	430	390	100	25	290	250	64	2.5
78	80	130/80	400	370	100	27	270	260	70	2.6
109	34	120/70	640	600	130	21	470	240	40	1.8
32	29	105/70	500	470	100	20	370	220	47	2.2 Tetany
62	81	140/70	420	380	100	26	280	250	66	2.5 Hemiplegia
112	64	130/90	620	470	120	25	350	320	70	2.6 Ca. of rectum
High		S 140 D 90			130	27		320	72	3.2
Low		S 105 D 70			100	20		220	40	1.8
Average		S 127 D 77			110	23		275	60	2.5

Pulse Pressure High 70, Low 35, Average 50

* After the removal of humin and amide nitrogen

The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen

M/B ratio was slightly higher than normal, being in 10 cases (91 per cent) between 1.0 and 2.9

NITROGEN DISTRIBUTION IN HYPERTENSION

In experimental hypertension, as previously stated, the changes in the nitrogen distribution of the serum proteins are in (a) the basic amino nitrogen, (b) the mono-amino nitrogen, or (c) in both. In hypertension in man similar changes have been found and the cases grouped accordingly.

Group A Hypertension with a lowered basic amino nitrogen, an increased mono-amino nitrogen, and an increased M/B ratio.

The data in a series of 18 cases showing a change in both nitrogen fractions are given in table 3. The ages of the individuals varied between 24 and 77 years, with an average of 56. The range of the systolic blood pressure varied between 165 and 286, with an average of 208, and the diastolic pressure varied from 70 to 142, with an average of 101. The pulse pressure varied between 65 and 200, with an average of 106.

The basic amino nitrogen varied between 60 and 90 mg. with an average of 75 mg. and formed between 10 and 21 per cent with an average of 15 per cent of the total nitrogen after hydrolysis. The mono-amino nitrogen ranged between 330 and 590 mg. with an average of 462 mg. This fraction forms between 73 and 100 per cent with an average of 83 per cent of the total nitrogen after hydrolysis. The M/B ratio was the highest obtained of all the cases of hypertension studied, varying between 3.6 and 9.8 with an

average of 57. A comparison of the data obtained in this group with that of the normals shows a definite alteration in the nitrogen distribution.

One exception was encountered. Case 55, a male aged 42 years, with blood pressure of 128 systolic and 60 diastolic, whose nitrogen distribution was similar to that observed in the cases of hypertension. This individual had a neurosis and was considerably overweight. The urine was negative and there was no evidence of nitrogen retention in the blood. The blood

TABLE III

Nitrogen Distribution of Serum Proteins in Hypertension Cases Showing Decreased Basic Amino Nitrogen and Increased Mono-Amino Nitrogen and M/B Ratio

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm Hg	mg per 100 c c				mg per 100 c c			
30	49	165/90	500	440	90	20	350	350	80	3.9
84	52	170/95	730	480	80	17	370	360	75	4.5
85	44	208/118	666	580	60	10	600	590	100	9.8
89	67	190/110	550	490	70	14	420	420	86	6.0
91	64	210/105	800	600	70	12	550	550	90	7.8
92	62	185/120	660	640	80	12	580	490	76	6.1
93	49	210/100	590	560	60	11	500	500	89	8.3
94	61	190/80	650	500	70	14	430	430	86	6.1
95	36	200/100	620	520	70	13	450	420	80	6.0
96	42	220/140	530	500	80	16	420	410	82	5.1
97	24	170/70	570	500	80	16	420	420	84	5.2
98	74	236/84	640	610	70	11	540	500	82	7.1
99	55	286/86	560	500	80	16	420	420	80	5.2
87	41	224/142	710	460	70	17	390	390	84	5.5
60	77	220/90	500	480	80	17	400	400	83	5.0
34	70	230/100	450	420	90	21	330	330	80	3.6
36	68	205/100	450	430	80	18	350	330	76	4.1
61	74	200/100	520	490	80	16	410	360	73	4.5
High		S 286 D 142			90	21		590	100	9.8
Low		S 165 D 70			60	10		330	73	3.6
Average		S 208 D 101			75	15		426	83	5.7
Nonhypertensive										
55	43	128/60	500	450	80	18	370	360	80	4.5 Neurosis Hyperthyroid

Pulse Pressure for hypertensive cases: High 200, Low 65, Average 106

* After the removal of humin and amide nitrogen

The M/B ratio means the ratio of the mono amino nitrogen to the basic amino nitrogen

serum cholesterol was 145 mg per 100 c c and the basal metabolic rate was plus 14 per cent. There was no previous history of hypertension.

Group B Hypertension with a decrease in the basic amino nitrogen and no changes in the mono-amino nitrogen.

The data of the examinations in the 14 cases comprising this group are given in table 4. The age of the patients varied between 22 and 83 with an average of 62 years. The systolic blood pressure varied between 150 and 230 with an average of 180, while the diastolic pressure varied between 80 and 120 with an average of 100. The pulse pressure range was between 50

and 120 with an average of 81. The basic amino nitrogen values varied between 70 and 90, with an average of 84 mg, thus, this fraction varied between 13 per cent and 25 per cent with an average of 19 per cent of the total nitrogen after hydrolysis. The values for the basic amino nitrogen and the percentage of the total nitrogen after hydrolysis were slightly higher than those in group A.

While the mono-amino nitrogen values were within normal limits, the per cent this fraction formed of the total nitrogen after hydrolysis is lower

TABLE IV
Nitrogen Distribution of Serum Proteins in Hypertension Cases Showing a
Decreased Basic Amino Nitrogen

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen * after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm Hg	mg per 100 c c				mg per 100 c c			
37	73	230/120	430	410	90	22	320	300	73	3.3
38	70	190/105	520	500	90	18	410	270	54	3.0
45	73	150/95	500	480	90	19	390	310	64	3.4
46	72	150/90	550	520	70	13	450	310	60	4.4
47	30	145/90	490	470	90	19	380	310	66	3.4
65	60	195/100	400	370	70	18	300	300	81	4.3
66	22	150/95	440	410	90	22	320	290	70	3.2
68	72	210/110	420	390	80	20	310	300	77	3.7
69	82	210/90	470	450	70	15	380	270	60	3.8
71	67	198/90	400	370	90	24	280	280	75	3.1
72	70	150/80	440	410	90	22	320	290	70	3.2
74	70	160/90	400	360	90	25	270	270	75	3.0
70	72	190/100	500	470	80	19	390	220	46	2.7
108	56	178/120	550	470	90	19	380	220	47	2.4
High	82	S230 D120			90	25		310	81	4.4
Low	22	S150 D 80			70	13		220	46	2.4
Average	62	S180 D100			84	19		281	65	3.4

Pulse Pressure High 120, Low 50, Average 81

* After the removal of humin and amide nitrogen

The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen

than those of group A, but higher than the normal group. The actual values varied between 220 and 310 mg with an average of 281 mg. The M/B ratio varied between 2.4 and 4.4 with an average of 3.4. These values, while not as high as those in group A, are increased over the normal.

Group C Hypertension in which there is an increase in the mono-amino nitrogen fraction only.

The largest number of our hypertensive cases are those in which there was a rise in the mono-amino nitrogen only. The data of these cases are

given in table 5 The group comprises 32 cases, the ages ranging between 26 and 87 with an average of 56 years The systolic blood pressure varied

TABLE V

Nitrogen Distribution of Serum Proteins in Hypertension Cases Showing Increased Mono-Amino Nitrogen

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm Hg	mg per 100 c c				mg per 100 c c			
2	50	164/100	650	630	120	20	510	500	79	4 1
7	67	180/102	560	540	100	18	440	430	80	4 3
14	51	195/110	630	620	110	17	510	500	80	4 5
17	42	235/140	550	530	120	22	410	400	75	3 3
19	46	205/118	750	730	130	17	600	580	80	4 4
20	39	152/80	530	520	120	23	400	360	70	3 0
22	26	155/85	560	540	120	22	420	400	74	3 3
23	79	155/82	650	630	120	19	510	500	80	4 1
31	69	170/90	540	500	100	20	400	360	72	3 6
33	69	210/100	550	530	120	22	410	380	71	3 1
39	87	235/120	500	480	110	23	370	330	70	3 0
42	71	195/70	600	570	140	24	430	430	75	3 0
43	69	200/100	600	570	120	21	450	450	80	3 7
49	65	210/115	530	500	110	22	390	400	80	3 6
51	79	230/115	540	520	100	19	420	400	77	4 0
54	78	195/75	500	480	110	23	360	360	75	3 2
75	31	250/160	520	480	110	23	360	340	71	3 1
86	27	156/92	600	440	100	22	340	330	75	3 3
88	38	182/116	950	710	110	15	580	580	81	5 2
90	60	210/105	1020	850	110	13	740	750	88	6 8
100	54	180/80	500	480	120	25	360	360	75	3 0
101	40	194/108	750	700	130	19	570	570	81	4 3
102	64	215/120	990	770	148	19	620	620	80	4 1
103	47	160/50	600	580	130	22	460	510	88	3 9
6	49	156/94	510	490	110	22	370	360	73	2 2
107	53	234/156	660	590	180	30	400	420	71	2 3
104	42	188/116	650	610	190	31	420	390	64	2 0
105	52	210/110	550	490	150	30	340	340	70	2 2
67	73	200/110	520	500	160	32	340	330	66	2 0
52	74	172/82	600	560	130	23	430	360	64	2 7
11	45	156/100	520	500	120	24	380	350	80	2 9
48	74	230/120	540	510	100	19	410	330	64	3 3
High	87	S250 D 160			190	32		750	88	6 8
Low	26	S152 D 50			100	13		330	64	2 0
Average	56	S193 D 103			123	22		428	75	3 5

Pulse Pressure High 120, Low 56 Average 89

Nonhypertensive

12	17	106/61	550	530	160	30	370	360	68	2 1	Splenectomy
13	20	106/66	540	520	120	23	400	360	69	3 0	"
29	55	100/60	550	530	110	20	420	400	75	3 6	"
16	56	118/60	500	480	100	20	380	360	75	3 6	Per anemia
21	55	108/58	560	540	120	20	420	400	74	3 3	Abse of liver
											Acute uremia
26	33	115/78	650	640	120	19	520	510	80	4 2	Hodgkin's dis
											Scl of aorta
24	64	110/90	540	520	120	23	400	390	75	3 2	Hyper prostate

* After the removal of humin and amide nitrogen

The M/B ratio means the ratio of the mono-amino nitrogen to the basic amino nitrogen

between 152 and 250 with an average of 193, and the diastolic pressure varied between 50 and 160 with an average of 103 The pulse pressure ranged between 56 and 120 with an average of 89 The basic amino nitro-

gen varied between 100 and 190 with an average of 123 mg and formed from 13 per cent to 32 per cent with an average of 22 per cent of the total nitrogen after hydrolysis. The mono-amino nitrogen fraction varied between 330 and 750 mg with an average of 428 mg, as compared with an average of 269 mg for the normal group. This fraction represents between 64 per cent and 88 per cent of the total nitrogen after hydrolysis with an average of 75 per cent as compared with an average of 54 per cent obtained for the normal group. The M/B ratio varied between 2.0 and 6.8 with an average of 3.5 as compared with an average of 1.9 for the normal group.

Exceptions There were seven individuals with normal blood pressure whose nitrogen distribution showed an increase in the mono-amino nitrogen fraction. Among these were three cases from which the spleen had been removed, and one each of pernicious anemia, abscess of the liver complicated with acute uremia, hypertrophied prostate, and Hodgkin's disease. The mono-amino nitrogen values of these nonhypertensive cases varied between 360 and 510 mg with an average of 354 mg. The M/B ratio varied between 2.1 and 4.2 with an average of 3.1.

Group D Hypertension with normal nitrogen distribution

In table 6 are given the data on 12 cases of hypertension in which there were no significant changes from the normal in the nitrogen distribution of

TABLE VI
Cases of Hypertension Showing Normal Nitrogen Distribution

Case	Age	Blood Pressure	Total Nitrogen	Total Nitrogen* after Hydrolysis	Basic Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	Total Nitrogen of the Phosphotungstic Acid Filtrate	Mono-Amino Nitrogen	Percentage of Total Nitrogen after Hydrolysis	M/B Ratio
		mm Hg	mg per 100 c c				mg per 100 c c			
25	34	185/138	450	430	110	25	300	300	70	2.7 Arteriosclerosis
35	70	190/85	590	560	100	18	460	250	44	2.5 Obesity
41	69	225/90	500	480	100	20	380	290	60	2.9 Arteriosclerosis
53	67	205/110	520	490	100	20	390	320	65	3.2 Myocarditis
57	71	230/100	500	370	100	27	270	240	67	2.4 Arteriosclerosis
58	80	200/70	520	490	110	22	380	300	61	2.7 Obesity
106	49	252/140	570	490	150	30	330	310	63	2.0 Arteriosclerosis
110	16	138/90	560	500	160	32	340	250	50	2.0 Uremia
63	73	170/70	470	450	120	26	330	230	51	1.5 Chr tonsillitis
73	68	220/190	470	440	100	22	330	290	66	2.9 Arteriosclerosis
50	75	160/70	570	550	120	22	430	300	54	2.5 Arteriosclerosis
56	6	117/82	440	420	110	25	310	250	60	2.2 Diabetes
										Acute hem nephritis
High		S 252 D 190			160	32		320	70	3.2
Low		S 117 D 70			100	18		230	44	1.5
Average		S 191 D 94			115	24		277	59	2.4

Pulse Pressure High 135, Low 35, Average 96

* After the removal of humin and amide nitrogen

The M/B ratio means the ratio of the mono amino nitrogen to the basic amino nitrogen

the serum proteins. The systolic blood pressure of this group varied between 117 and 252 with an average of 191, the diastolic pressure between 70 and 190 the average being 94, while the pulse pressure varied between 35 and 135 with an average of 96.

DISCUSSION

In 84 per cent of the cases of hypertension which we have studied there were definite changes in the nitrogen distribution of the serum proteins. When either the basic amino or mono-amino nitrogen fractions were altered, the degree of hypertension was about the same as determined by the averaged systolic and pulse pressures. These averaged pressures, however, were higher when both nitrogen fractions were involved in the change. This suggests some correlation between the degree of hypertension and the nitrogen distribution, although the exact relationship cannot be stated at the present time. From the results of animal experimentation,¹ hypertension seems to precede changes in the M/B ratio.

Although the majority of the cases of hypertension showed a change in the nitrogen distribution, there were 12 cases in which no change was demonstrable. In most of these exceptions the dominant clinical complaint was that of atherosclerosis rather than hypertension. In other hypertensive individuals in whom alterations in the M/B ratio was observed, atherosclerosis was not the dominant clinical complaint.

In previous work¹ an extensive fibrosis of the spleen was noted in animals suffering from aspartic acid induced hypertension, and it was pointed out that fibrotic changes also occurred in the spleen of human cases suffering during life with hypertension. It is interesting to note in the light of these observations that in five of the seven nonhypertensive cases exhibiting an altered nitrogen distribution, disturbances in the reticulo-endothelial system were evident. In three of these cases the capacity of the reticulo-endothelial system was greatly reduced by removal of the spleen, another suffered from pernicious anemia, a condition in which the spleen shows marked fibrotic changes, and the fifth from Hodgkin's disease which broadly considered is a lesion of the reticulo-endothelial system. These changes which occurred in (a) the spleens of hypertensive animals, (b) the spleens of human cases dying of hypertension and (c) in the reticulo-endothelial system of non-hypertensive cases suggests that the reticulo-endothelial system or the spleen plays a rôle in maintaining the M/B ratio at a normal level.

In the cases of hypertension with a low basic amino nitrogen, there was little or no evidence of nephritis. A review of the clinical aspects of the cases of hypertension having increased mono-amino nitrogen showed in the greater majority of the patients a mild degree of nephritis without retention of the non-protein nitrogenous constituents. Four of the cases, however, showed slight nitrogen retention. In the group of hypertensive cases in which both nitrogenous fractions deviated from the normal, there was us-

ually evidence of a marked nephritis with nitrogen retention in the blood to a varying degree

On the basis of the chemical and clinical studies in the group of hypertensive cases reported in this paper, the following classifications appear possible

Class 1 Hypertensive individuals whose blood serum proteins showed a decreased basic amino nitrogen and an increased mono-amino nitrogen. This group showed evidence of a severe nephritis with moderate non-protein nitrogen retention in the blood which occasionally was severe

Class 2 Cases of hypertension in which the blood serum proteins showed a low basic amino nitrogen, no change in the mono-amino nitrogen fraction and little or no evidence of nephritis

Class 3 Cases of hypertension in which only the mono-amino nitrogen fraction of the blood serum proteins was increased. This group showed a moderate nephritis, occasional nitrogen retention, with little or no evidence of arteriosclerosis

Class 4 Cases of hypertension in which the basic amino and mono-amino nitrogen fractions were within normal limits. These cases showed arteriosclerotic changes and symptoms. This group did or did not have evidence of kidney impairment

On the basis of the classifications outlined above, one might readily speculate both as to the etiology of hypertension and as to therapeutic possibilities. It might be that the changes noted in the nitrogen distribution are due to a functional disturbance of the reticulo-endothelial system. Organotherapy of the reticulo-endothelial system might prove to be of therapeutic benefit alone, or in combination with dietary changes. It is possible that the hypertension might disappear if the ratio between these two nitrogen fractions could be restored to normal by raising the basic amino nitrogen. In the animal experiments as reported elsewhere,¹ the mono-amino nitrogen values dropped when the injections of aspartic acid were discontinued and the blood pressure returned to normal. It is within the realm of possibility to raise the basic amino nitrogen values by suitable changes in the diet

CONCLUSIONS

1 Changes from the normal were observed in 84 per cent of 76 cases of hypertension in either the basic amino or mono-amino nitrogen fractions of the blood serum proteins or in both these fractions, the change in 23 per cent was in both fractions, in 18 per cent only the basic amino nitrogen was altered, in 42 per cent the mono-amino nitrogen alone was changed and in 15 per cent no change in either fraction was demonstrable

2 Based upon these chemical changes, a classification of cases of hypertension is proposed. The more exact details of the various groups are given in the body of the paper

REFERENCES

- 1 RAFSKY, H A , BERNHARD, A , and ROHDENBURG, G L Studies in hypertension I The production of experimental hypertension and a correlated effect upon the nitrogen distribution of the blood proteins, *Am Jr Med Sci* , 1935, cxc, 187
 - 2 BERNHARD, A , LEOPOLD, J S , and DREKTER, I J Blood proteins of children, distribution of total nitrogen in whole blood, red blood cells and serum proteins from same specimen, *Am Jr Dis Child* , 1934, xlvii, 1256-1260
- BERNHARD, A , LEOPOLD, J S , and DREKTER, I J Blood proteins of children, distribution in same specimen of blood of hydrolyzable, amide, humin, basic amino and mono amino nitrogen of whole blood, red cells and serum proteins, *Am Jr Dis Child* , 1934, xlviii, 819-829

SEDIMENTATION TIME IN ACUTE CARDIAC INFARCTION *

By CHARLES SHOOKHOFF, M D , ALBERT H DOUGLAS, M D , and MEYER A RABINOWITZ, M D , *Brooklyn, N Y*

IN 1931 the authors reported 10 cases of acute cardiac infarction secondary to coronary artery thrombosis in which the red blood cell sedimentation time was studied¹ Burak² subsequently reported a similar study, but the literature on the subject has, in general, been scant Singer³ and Wollheim⁴ have both mentioned the increased rapidity of red cell sedimentation rate as a diagnostic factor in coronary thrombosis Because the sedimentation time has frequently been of great help to us in the diagnosis and treatment of acute coronary thrombosis, we are reporting an additional series of cases studied during the past three years

METHOD

The sedimentation times were done according to the method of Linzenmeier⁵ Sixty minutes has been taken as the lower limit of normal, i.e. sedimentation more rapid than 60 minutes to the 18 mm mark is regarded as abnormal No corrections were made for variations in the red blood cell count, but this did not appear to make a serious difference in this series

Twenty-nine cases of acute coronary thrombosis were studied In all cases included in this series, the clinical diagnosis was confirmed by electrocardiography Of nine patients who died, five were autopsied, and an acute coronary thrombosis found Cases which had complicating disease which might influence the sedimentation rate were excluded

RESULTS

In *all* the cases studied the sedimentation time was abnormally rapid at some time during the course of the disease In all the cases but one, the rate was abnormally rapid by the fifth day In the one exception the figure did not go below 60 minutes until the second week, but even in this case a drop was apparent toward the end of the first week (Chart 1) In several cases the sedimentation time became abnormal as early as the second day (Chart 2) The earliest in this series at which the sedimentation time returned to normal was the thirteenth day, and the latest, the thirty-ninth day At times it was kept rapid over a rather long period by repeated thromboses (Charts 2 and 3)

In two cases the temperature and leukocyte count were normal throughout while the sedimentation time was definitely abnormal In most of the

* Received for publication April 23, 1935

From the Division of Cardiology, the "B" Medical Services, the Jewish Hospital of Brooklyn

CHART I
A S, Male, Aged 42 Years

Day of Illness	Date	Maximum Temp	Maximum Pulse	White Blood Count	Polys	Sedimentation Time to 18 mm
2	4-29-31	99.2	84			270 minutes
3	4-30-31	99.4	108	16,800		
4	5-1-31	99.8	128			135 minutes
5	5-2-31	100.4	116			
6	5-3-31	99.8	104	15,800	66%	65 minutes
7	5-4-31	99.4	104			
8	5-5-31	99.2	96	11,100	55%	60 minutes
9	5-6-31	99.6	80			
10	5-7-31	99.4	78			
11	5-8-31	99.6	78	10,700	63%	49 minutes
12	5-9-31	99.6	82			
13	5-10-31	99.6	84			
14	5-11-31	99.2	86	10,100	51%	55 minutes
15	5-12-31	98.8	84			
16	5-13-31	98.8	80			
17	5-14-31	98.8	84	9,850	51%	60 minutes
18	5-15-31	99.2	86			
19	5-16-31	98.8	76			
20	5-17-31	99.2	80			
21	5-18-31	99.0	82	8,500	58%	90 minutes

Remarks Closure on April 28, 1931

Hemoglobin 90%

R B C, 4,700,000

Electrocardiograms Inversion of T-wave in all leads Later T-wave became positive, and a left axis deviation developed

CHART II
S H, Male Aged 54 Years

Day of Illness	Date	Maximum Temp	Maximum Pulse	White Blood Count	Polys	Sedimentation Time to 18 mm
3	11-12-32	99.4	102	7,400	69%	55 minutes
13	11-22-32	99.0	90			37 minutes
17	11-26-32	98.6	84			30 minutes

Remarks First closure on November 8, 1932

Hemoglobin 80%

R B C, 4,250,000

2	6-28-33	98.2	100			40 minutes
3	6-29-33	99.6	106	18,600	75%	
8	7-6-33	99.4	96	18,000	67%	
15	7-13-33	104.0	104			43 minutes
22	7-20-33	99.4	104			60 minutes
28	7-26-33	98.6	96	7,800	68%	45 minutes
37	8-4-33	99.0	90			52 minutes
42	8-9-33	98.6	90			50 minutes
49	8-16-33	98.6	96			85 minutes

Remarks Second closure on June 26, 1933

Hemoglobin 85%

R B C, 3,350,000

Electrocardiograms November 19, 1932 Left axis deviation Q-R-S slurred S T isoelectric T₁ sharply inverted, T₂ and T₃ upright

June 28, 1933 Definite Q₂-T₃ type S-T₂ and S-T₃ markedly elevated, S-T₁ depressed T₁ upright, T₂ and T₃ sharply inverted

CHART III
L G, Female, Aged 61 Years

Day of Illness	Date	Maximum Temp	Maximum Pulse	White Blood Count	Polys	Sedimentation Time to 18 mm
2	10-14-32	102 0	140	11,800	79%	29 minutes
3	10-15-32	101 6	110			
4	10-16-32	101 0	92			
12	10-24-32	100 4	92	9,600	74%	23 minutes
15	10-27-32	100 2	90			
20	11- 1-32	99 4	96	9,600	66%	21 minutes
23	11- 4-32	99 0	94			
27	11- 8-32	100 2	90			21 minutes

Remarks Multiple thromboses, first one on October 13, 1932

Hemoglobin 65%

R B C, 3,600,000

Electrocardiograms October 18, 1932 Left axis deviation Occasional ventricular extrasystoles
Marked slurring of the Q-R-S

Repeated on November 1 and 15 without any essential change

cases there were fever and leukocytosis during the first few days at which time the sedimentation rate was normal. Toward the end of the first week the temperature and leukocyte count returned to normal while the sedimentation rate became definitely abnormal. The sedimentation rate then continued rapid for several weeks while the temperature and leukocyte count remained normal. Typical cases are illustrated in charts 4 and 5.

CHART IV
H S, Male, Aged 48 Years

Day of Illness	Date	Maximum Temp	Maximum Pulse	White Blood Count	Polys	Sedimentation Time to 18 mm
7 days prior to closure						More than 120 minutes
2	10-10-33	98 6	92	8,000	71%	
4	10-18-33	102 4	120	17,200	88%	
7	10-20-33	101 0	110			15 minutes
10	10-24-33	98 6	82			
14	10-27-33	98 6	90	9,500	61%	
20	10-31-33	100 0	110			45 minutes
22	11- 6-33	99 0	80			85 minutes
	11- 8-33	98 6	80			More than 120 minutes

Remarks Admitted because of severe angina of effort

Closure in hospital on October 17, 1933

Hemoglobin 86%

R B C, 4,600,000

Electrocardiograms October 10, 1933 Slurring of Q-R-S S-T is isoelectric T₁, T₂ upright, T₃ inverted

October 20, 1933 R-T segment in Leads I and II markedly elevated, arising from the downstroke of "R"

November 1, 1933 R-T is isoelectric T₁ sharply inverted, T₂ and T₃ are upright

CHART V
J M , Male, Aged 47 Years

Day of Illness	Date	Maximum Temp	Maximum Pulse	White Blood Count	Polys	Sedimentation Time to 18 mm
3	9- 6-32	101.4	108	24,000	78%	120 minutes
4	9- 7-32	101.6	112			
5	9- 8-32	100.8	100			
6	9- 9-32	100.8	92			
7	9-10-32	100.2	86			
8	9-11-32	100.4	88	8,000	64%	19 minutes
9	9-12-32	100.0	86			
10	9-13-32	99.0	96			
11	9-14-32	99.0	88			
12	9-15-32	99.0	90			
24	9-27-32	100.0	80	8,400	72%	20 minutes
29	10- 2-32	100.0	80			160 minutes 170 minutes

Remarks Closure on September 4, 1932

Hemoglobin 100%

R B C , 6,510,000 (Emphysema probable cause of slight polycythemia)

Electrocardiograms September 10, 1932 Q-R-S slurred R-T₁ and R-T₂ markedly elevated T-wave is upright

September 28, 1932 T₁ and T₂ sharply inverted, T₃ upright R-T₁, R-T₂ and R-T₃ isoelectric and somewhat rounded

October 4, 1932 As before, except for inversion of T₃ as well as of T₁ and T₂

DISCUSSION

Patients not infrequently present themselves with a history of an attack of angina pectoris occurring several days or even several weeks previously which arouses suspicion of a recent coronary artery thrombosis. The temperature and blood count are usually normal at this time, and the electrocardiogram may frequently be indefinite. It is in these cases that we have found the sedimentation time to be of great help, and where an electrocardiograph is not available, the increased sedimentation rate may be the only definite evidence of active cardiac muscle involvement.

Even where the diagnosis is clear, we believe it is of definite value to follow the sedimentation time. We have found it to be a sensitive indicator of subsequent thrombosis in the heart or elsewhere, or of embolus or infection. (Chart 5) It enables one, too, to estimate the rapidity of healing. At the present time there is no definite evidence that the rapidity of the sedimentation time is proportionate to the extent of the damage in the heart, but it seems justifiable to assume that while the determination is abnormal, active changes are taking place in the heart muscle. We believe that the sedimentation time makes less arbitrary the duration of bed rest for a particular case and that a patient with an acute coronary closure should be kept in bed at least until this determination has returned to normal. We wish to emphasize the importance of a careful search for infection or infarction outside the heart before a cardiac significance is attached to a rapid sedimentation rate.

CONCLUSIONS

- 1 The red blood cell sedimentation time was studied in 29 cases of acute cardiac infarction. It was abnormally rapid in all.
- 2 It became rapid between the second and fifth days and returned to normal between the thirteenth and thirty-ninth days.
- 3 An abnormal sedimentation rate may outlast the return of temperature and leukocyte count to normal by as much as four weeks. It may be abnormal when the temperature and leukocyte count have been normal throughout.
- 4 It is of great help in cases seen first several days or weeks after the occurrence of a cardiac infarction.
- 5 It helps in the recognition of subsequent thrombosis or infection.
- 6 It makes less arbitrary the duration of bed rest.

REFERENCES

- 1 RABINOWITZ, M., SHOOKHOFF, C., and DOUGLAS, A. H. The red cell sedimentation time in coronary occlusion, *Am Heart Jr*, 1931, vii, 52.
- 2 BURAK, M. Die Bedeutung der Senkungsgeschwindigkeit für die Diagnose des akuten Coronarverschlusses, *Wien klin Wchnschr*, 1934, xi, 327.
- 3 SINGER, R. Zur Klinik der Coronar-Thrombose, *Wien klin Wchnschr*, 1934, xlvii, 810.
- 4 WOLLHEIM, E. Herzinfarkt und Angina pectoris, *Deutsch med Wchnschr*, 1931, lvii, 617.
- 5 LINZENMEIER, G. Die Blutkörperchensenkungsgeschwindigkeit als differential diagnostisches Hilfsmittel bei adnexerkrankungen, *Zentralbl f Gynak*, 1922, xli, 555. Untersuchungen über die Senkungsgeschwindigkeit der roten Blutkörperchen, *Pflüger's Arch f d gesamt Physiol*, 1921, clxxvi, 272. Neue Untersuchungen über die Senkungsgeschwindigkeit der roten Blutkörperchen, *Zentralbl f Gynak*, 1921, xlv, 347.

COMBINED MEDICAL AND SURGICAL MANAGEMENT OF PEPTIC ULCER, WITH EMPHASIS ON THE TREATMENT OF HEMORRHAGE *

By J W THOMPSON, M D , F A C S , and H W SOPER, M D , F A C P ,
St Louis, Missouri

THE first pre-requisite for an intelligent approach to the treatment of peptic ulcer by any method is an accurate conception of the pathologic changes in the gastroduodenal mucous membrane which are designated as "peptic ulcer" This term has been applied to all variations of pathologic changes from a simple erosion of the mucosa to a deep penetrating lesion with attachments to the neighboring viscera The confusion that exists in the general medical mind relative to peptic ulcer can be directly attributed to the fact that frequently the disputants have entirely different lesions in mind Then strangely enough the disease seems to vary in different races both in incidence and severity The Hebrew evidently is more prone to peptic ulcer and its complications than is the Aryan Walters and Snell,¹ who are quite familiar with the clinical and surgical manifestations of ulcer in the United States, observed that the central European nations present a different anatomico-pathologic picture from that seen in this country The Austrian peoples are more prone to multiple ulcerations combined with a severe chronic gastritis, whereas the lesion most often seen in America is a single localized area of inflammatory change with the remainder of the mucosa in an approximately normal state The important point then in any discussion of peptic ulcer is to so focus the attention that everyone has the identical pathologic process in mind

The experience of the authors has been chiefly comprised of patients from the middle western United States, most of whom have been of northern European origin but including a liberal number of Semitic descent Peptic ulcer in these peoples is usually confined in number to a single lesion and is more frequently situated in the duodenum than in the stomach It has been our observation that multiple ulceration when it occurs is more common in the duodenum

Therefore, for the purposes of this paper we will define peptic ulcer as solution in the continuity of the gastroduodenal mucosa, varying between lesions of minute size and confined superficially to the mucosa, and the larger, punched out, characteristic ulceration with a definite crater and a base that is comprised of scar tissue of variable extent These lesions may be multiple, especially in the duodenum, and have a distinct tendency to heal and recur periodically with an increasing deposit of cicatrix after each episode As the process advances, perforation through the walls of the stomach

* Read at Regional Meeting of the American College of Physicians, Springfield, Illinois, September 24, 1935 Received for publication October 7, 1935
From the Soper-Mills Clinic

or duodenum may take place, at times quite rapidly and in other instances over prolonged periods of time. During this process attachment to neighboring viscera or even perforation into them may occur.

The etiology of peptic ulcer still remains unproved. The experimental surgeons have presented evidence that ulcer is due to acid gastric secretions acting on the mucous membrane that lacks some neutralizing factor to adjust the fine physiologic balance between the secretions and enzymes of the digestive juices of the stomach, duodenum, pancreas and liver. Mann and Williamson² have produced experimentally so-called surgical duodenal diaphragm peptic ulcers in dogs that are indistinguishable histologically from those found in humans. Quite recently Bollman and Mann,³ corroborating the experiments of Von Wagoner and Churchill,⁴ have described ulcers produced in dogs by prolonged ingestion of the drug cinchophen. These ulcerations are likewise quite similar to those seen clinically.

The healing process in ulcer of the stomach and duodenum is an exact counterpart of that observed in varicose ulcer of the leg. The crater of the ulcer is gradually filled in with fibrin, and the epithelial edges proliferate toward the center, gradually closing the defect. Just as the varicose ulcer of the lower leg needs to be protected from traumatization of the delicate, tender, fragile, advancing margin of newly forming epithelium, so does the ulcer of the gastroduodenal mucosa need to be guarded. The slightest trauma will dislodge the plug of fibrin in the base of the crater, disrupting the newly forming glandular epithelium and leaving the base vulnerable to the acid gastric secretions. These points were admirably demonstrated in the experimental work of Mann⁵ presented at a recent Hodgen lecture. The practical clinical application is obvious.

Malignant degeneration of peptic ulcer of the gastric mucosa is a distinct possibility. It practically never happens in the duodenal lesion. McCarty⁶ long ago advanced the theory of metaplasia from peptic ulcer to gastric cancer. Therefore, ulcer of the stomach must be classified as benign or malignant. Alvarez⁷ has stated that any gastric ulcer larger than a dime is potentially malignant, and gastric resection should be seriously considered in such patients no matter what the age may be.

The association of gastric and duodenal ulcer in the same patient is of frequent occurrence, and the possibility of a carcinoma of the stomach should always be kept seriously in mind in any case of duodenal ulcer presenting a persistent occult blood reaction in the feces. It is quite possible that there may be roentgen-ray evidence of deformity in the duodenal cap or in the region of the pylorus, and that a severe hemorrhage from a gastric cancer may be mistakenly attributed to the old ulcer in the duodenum. The following case history strikingly illustrates this point.

Mrs. Ursula M., aged 45, a married woman, presented herself at the clinic complaining of dyspepsia and belching accompanied by a burning sensation in the epigastric region. General physical examination revealed that she was of the asthenic type with visceroptosis. Examination of the feces by the guaiac test showed occult

blood present persistently despite adequate medical treatment. The patient was advised to have surgical exploration because of this but refused to consider it. In addition there was a filling defect of a seemingly benign nature at the pyloric ring. No evidence of filling defect in the stomach was observed. While under observa-

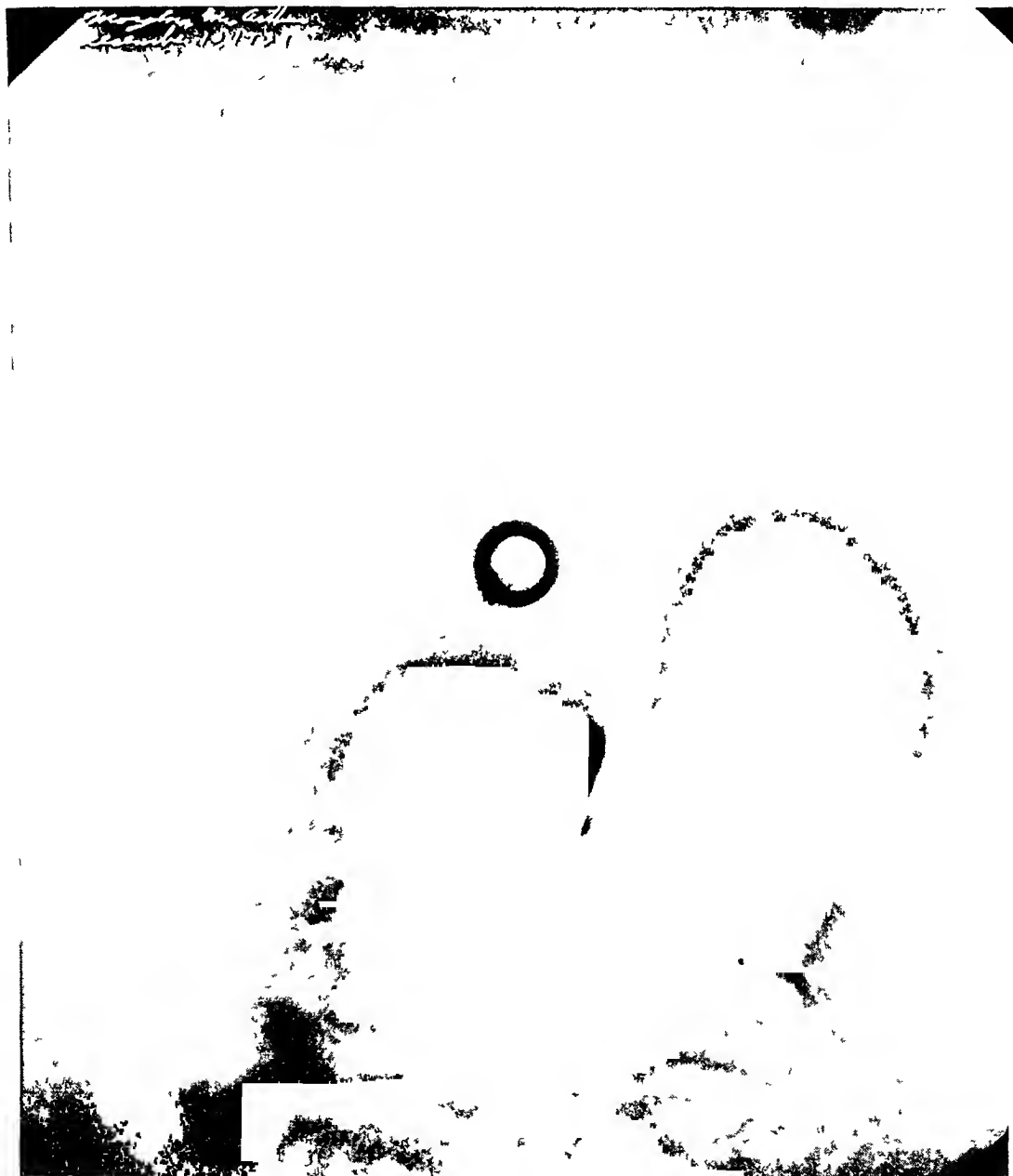


FIG 1 Roentgenogram demonstrating atonic stomach with duodenal ulcer (Note smoothness of outline of both greater and lesser curvature)

tion, and having refused elective operation, she was taken with a severe series of hemorrhages which depleted her circulation of blood until her erythrocyte count was approximately 1,200,000 and her hemoglobin 25 per cent (Dare). She was im-

mediately hospitalized and given three blood transfusions, while under the trans-nasal suction siphonage method of treatment for hematemesis. As soon as her condition permitted she was operated upon and the source of the bleeding was found to be not in the pyloric region as suspected (figure 1) but arising from the base of a shallow



FIG 2 Postoperative roentgenogram of same patient as in figure 1 following partial gastrectomy with removal of segment of stomach containing grade III carcinoma

gastric cancer situated on the greater curvature of the stomach. A partial gastrectomy was done removing approximately two-thirds of the stomach well above the growth. The patient made a good recovery and examination of the stools has been

negative Roentgen-ray films show the remaining portion of the stomach smooth in outline with no evidence of recurrence (figure 2)

This case is presented to demonstrate the association of gastric cancer with duodenal and prepyloric benign lesions. The roentgen-ray here did not disclose the lesion situated on the greater curvature of a large visceroprotic stomach. It is well to reiterate that a persistent occult blood reaction (guaiac) in the feces when the patient is on a meatless dietary regimen should always excite the suspicion of malignancy. Surgical exploration should be advised even in the absence of a lesion demonstrable by means of the roentgen-ray.

In complicated gastroduodenal ulcer the combination of a medically minded surgeon with a clinician who fully appreciates the advantages of surgery offers the patient the greatest chance of permanent relief. In the type of individual who has what we may term "ulcer diathesis" neither medical nor surgical treatment offers very promising results. These are the patients who have recurrent ulcerations after any and all types of surgery, gastric resection not excluded. The simple benign uncomplicated peptic ulcer of the gastroduodenal mucosa is the type amenable to successful treatment by a medical regimen of which there are innumerable variations.

Medical management of duodenal ulcer has been greatly simplified in recent years and placed on a more rational basis. There has been some tendency to make it difficult again by employing various hypodermic injections of organic compounds of histidine. Most of these methods are accompanied by careful dietetic instructions and it is of extreme uncertainty where to attribute the credit for any relief obtained. All tissues, more especially epithelial structures throughout the body, have an inherent biologic tendency to proliferate and heal over any break in their continuity. Hargis and Robertson⁸ demonstrated by postmortem studies on patients who succumbed to unrelated constitutional diseases that evidences of old healed scars of peptic ulcers were present when no mention had been made of gastric symptoms in the patients' chief complaints. Upon interrogation of the near relatives of these deceased patients it was learned that they did have "stomach trouble" (symptoms of peptic ulcer) for which they quite frequently never consulted a physician. Consequently, it is quite justifiable to conclude that there are many individuals who have mild peptic ulcers which undergo several periods of recurrence without causing severe symptoms.

The smooth diet, judiciously increased according to the progress of the patient's symptoms and combined with sedative drugs and alkalis to diminish hyperacidity, forms the orthodox rationalized basis of treatment founded on an accurate understanding of the fundamental pathologic processes involved and the physiologic resources of the patient required to promote healing of the lesions. In the acute stages a diet consisting chiefly of milk and cream, junket, thin cooked cereals, with cream and sugar added, forms the standard measure employed. The feedings are given in quanti-

ties of six to ten ounces every two hours. Diluted egg albumin alone often allays the severe symptoms. The frequent feedings serve to lower acidity and provide a smooth texture to the gastric contents and prevent trauma to the healing ulcer that might occur when foods of coarse fibrous nature are ingested. The coarse foods damage the growing epithelial coating of the healing ulcer and promote recurrence or delay complete recovery. The modern dietary, consisting of various combinations of raw vegetable and fruit fibers made up in so-called "salads" comprising tomatoes, celery, apples and carrots among other things, is a common cause of persistent gastric symptoms in ulcer patients. The eating of these things by an ulcer patient is comparable to a varicose vein patient treating his varicosities and concomitant ulcers by daily rubs with coarse sandpaper.

Since Marriott⁹ in 1929 advocated the use of evaporated milks in the feeding of young children, the senior author, H. W. S., began to employ them in the treatment of gastric and duodenal ulcer and ulcerative colitis. Milk as a source of bacterial infection in human beings, particularly in streptococcus sore throats and other infectious diseases, has been repeatedly emphasized. The work of Rosenow^{10,11} in this regard is highly significant. The splendid experimental work of Saunders¹² in demonstrating that milk is a possible etiologic factor in gastric and duodenal ulcer lends credibility to the belief that milk may possibly be a source of infection to individuals who are susceptible to a combination of factors leading to the development of peptic ulcer. Ross¹³ has reported a series of cases of peptic ulcer treated with the evaporated milks. The clinical observations of the author (H. W. S.) suggest that evaporated milks are a helpful adjunct in the dietary management of ulcer patients. Our diet lists have in recent years been modified to contain many raw fresh eggs which supply all the needed vitamins. A preliminary report of these observations has been published by Soper,¹⁴ and a more complete report of clinical observations with evaporated milk will be made later.

The administration of alkalis to ulcer patients has long been a matter of controversy. We no longer employ them extensively. The smooth diet, frequently fed, seems to be the secret of successful management. After two to three weeks on strictly soft foods the patient is permitted coddled eggs, increased amounts of cooked cereals, together with cottage cheese, toast with the crusts removed, creamed vegetable soups, ice cream, jello, baked or mashed potatoes, stewed fruits, white meat of chicken and tender broiled steaks or lamb chops.

A favorite sedative employed for many years with great satisfaction is a small dose of barbital (one grain) combined with atropine sulphate (one five-hundredth grain) together in a capsule with sugar or milk. The atropine is sufficient when taken three or four times daily to relieve pylorospasm, and the barbital is a very mild sedative. This prescription can be taken over protracted periods without harm or oversedation.

The more severe forms of benign gastric ulcer will occasionally require

hospitalization We have used with great satisfaction trans-gastric feedings by means of the indwelling Levin nasal catheter The tube is permitted to find its way into the jejunum, and a high caloric mixture is given through the tube, placing the stomach completely at rest This is the same principle as employed by Balfour¹⁵ in surgical jejunostomy minus the attendant surgical risk The nasal catheter is usually quite well tolerated by these cases after the first few hours of discomfort

The above outlined principles constitute the measures which we have employed in the medical management of peptic gastroduodenal ulceration Fortunately we have been consistently successful and see no reason for changing our methods Practically all patients can remain ambulant and employed Bleeding or hemorrhagic ulcer demands more detailed consideration

Soper¹⁶ in 1931 presented a method of treating hematemesis by means of the retention catheter Severe hemorrhage from a gastric or duodenal lesion benign or malignant is quite alarming, and often accompanied by shock Recovery frequently is prolonged Balfour,¹⁷ Bevan¹⁸ and Lahey¹⁹ all advise against immediate operation but reserve intervention for recurrent bleeding Practically all writers agree that blood transfusion is immediately indicated in all severe hemorrhages and that morphine hypodermically, blood coagulants, and complete bed rest are all essentials

The principle of keeping the stomach at absolute rest in order to allay bleeding from it or into it (as in the case of duodenal ulcer or esophageal varices) is physiologically sound, and borne out by practical experience in other comparable hollow viscera such as the urinary bladder Any quantity of liquid material in the stomach will incite peristalsis and provoke additional bleeding or prevent it from stopping The gastric wall and neighboring contractile viscera containing bleeding vessels must be absolutely quiet in order to promote clot formation and cessation of the hemorrhage Nature creates a vicious circle by virtue of the fact that the blood in large quantities escapes into the stomach, excites peristalsis and thereby accentuates the bleeding This process is comparable to a hemorrhage into the urinary bladder from any source The bladder fills up with clots and in the attempt by the hollow contractile organ to expell its contents tenesmus, spasm, overactive contraction and congestion are produced and the bleeding is aggravated The quickest method of relief here is to empty the bladder with a large catheter or an evacuator and place it at rest by an indwelling catheter and keep it at rest The analogy to hemorrhage into the stomach is entirely logical In spite of this one hears and reads of the so-called "expectant treatment of hematemesis" which consists of the administration of morphia and of letting the stomach do the best it can to get relief by vomiting or by expelling its contents into the intestinal tract It is to encourage the wider use of our method of gastric siphonage in the treatment of hematemesis that we wish to present in detail its employment and to reaffirm our satisfaction in its further use

By this method one has absolute control of the situation in gastric hemorrhage. The introduction of the tube is not uncomfortable to the patient if careful technic is used. The stomach is readily emptied of all clots and placed immediately at rest. Retching and vomiting such as are caused by lavage with a large tube are avoided, to the great satisfaction of the patient. A thromboplastic substance can be given hypodermically to promote coagulation in the bleeding vessel, and the same substance is of great advantage in the stomach itself, for seemingly it not only aids in stopping the bleeding but apparently causes the larger clots to be broken up into fine black particles so that they may be readily withdrawn through the nasal tube. Recurrent bleeding is readily detected by observing the washings, and the presence of acidity may be noted by testing with congo paper. The stomach can then be gently lavaged with a mild alkaline solution of soda bicarbonate to neutralize the acid secretion.

The following detailed points in the employment of this method are worthy of reiteration.

- 1 The technic of passing the tube is important. The nasal mucous membrane should be shrunk with a 2 per cent solution of cocaine hydrochloride. The Levin nasal catheter with several perforations in the distal six inches should be slowly passed down the esophagus and the patient allowed to take a swallow of water with each short advance of the tube. The glass pistoned syringe should be used often to keep the tube free of small clots. The tube may be permitted to drain by siphonage alone or may be attached to an apparatus to provide continuous suction, such as described by Ward,²⁰ Wangenstein,²¹ Orr²² and others. The character of the secretion passing through the tube should be observed frequently and tested for acid with fresh congo red paper. Liquid petrolatum is dropped along side of the tube through the nostril three times daily, and if the patient complains of sore throat a spoonful of liquid petrolatum may be given every one or two hours.

- 2 The use of a local hemostatic is important. We employ thromboplastic solution, injecting it undiluted directly into the stomach after the clots have been removed. The fine black clots that result are characteristic of this hemostatic.

- 3 The patient is usually thirsty, and we find that fresh egg albumin, water and gelatin water rarely excite acid secretion and can be safely permitted by mouth. Proctoclysis with a physiologic solution of saline and the intravenous injection of 2000 to 3000 c.c. of normal saline containing glucose in 5 to 10 per cent solution are continued for a period of three days. After that time the tube is permitted to find its way into the jejunum. This can be demonstrated by a roentgen-ray film. The patient is then fed a high caloric mixture and the stomach is still maintained at rest for a period of a week or 10 days according to the condition of the patient and the amount of discomfort caused by the nasal tube.

The obvious advantages of the method are its simplicity, and its value

in the removal of clots from the stomach and placing it at rest, the control of acidity, the easy detection of further bleeding, the elimination of nausea and vomiting and the maintenance of the patient's comfort. In addition the tube may be employed to give jejunal feedings and so maintain the stomach at rest for any desired period of time in accordance with the requirements of the individual patient.

Just which cases of peptic ulcer of the stomach and duodenum should be selected for surgical treatment has long been controversial. It is only through intelligent cooperation between the clinician and surgeon that the best interests of the patient are served. It is generally conceded that all uncomplicated cases of simple duodenal ulcer should be treated by a medical regimen, reserving surgical procedures for those cases which do not respond to the more conservative methods. In borderline cases the choice of method is frequently a matter for weighty decision. It is likewise conceded to be justifiable to use a medical regimen in the treatment of benign gastric ulcer. Emphasis must be placed on the dictum that any gastric ulcer which does not show an immediate response to diet and rest with a definite tendency to heal quickly, as shown by competent roentgenography, should be considered potentially malignant and recommended for surgery.

The successful surgical treatment of duodenal ulcer has been a great achievement. Relief of the patient's symptoms with minimal risk should be the goal rather than to subject him to a pre-determined type of operative procedure. It would seem obvious that extensive operations, such as gastrectomy and gastroduodenal resection, will carry a higher mortality in any surgical clinic than the more conservative procedure of gastro-enterostomy. We believe that the acid factor is the most important one in causation of ulcer. The reduction of acidity by a well functioning gastro-enterostomy certainly seems to be the more reasonable and conservative choice of procedure, especially since it is admitted that achlorhydria is secured in but 56 per cent of patients subjected to total or partial gastrectomy. These points were emphasized recently by Klein, Aschner and Crohn²³.

The choice of operative procedure, then, in duodenal ulcer should be made from a conservative point of view. The selection of procedure should be suited to the individual case and will vary according to the anatomic and pathologic characteristics of the ulcer and of the patient. The position of the stomach in the abdomen and its accessibility at the operating table will also influence the surgeon in his choice. In a series of 129 cases the author (J W T) found it justifiable to perform gastro-enterostomy on 87 patients whereas it was deemed advisable to choose pyloroplasty in but 17 of this series, pyloroplasty of Bilroth I type being employed in five cases. Partial gastrectomy was done in 18 instances for gastric ulcer. In 50 per cent of these the lesion proved to be malignant. The author (J W T) has never deemed it justifiable to perform extensive partial gastrectomy for duodenal ulcer but has conservatively employed the more physiological complete pylorotomy of Bilroth I type in five cases with uniformly satisfactory re-

sults Walters²⁴ recently stated that "the case for subtotal gastrectomy with removal of the duodenal ulcer remains one for further study, during which time gastro-enterostomy should continue to hold a position of high regard, for it will give good results at low operative risk in properly selected cases in which the response to a properly carried out medical regimen has been inadequate"

Proper selection of surgical cases requires experience and clinical judgment, and as an aid the following classification has been suggested

- 1 Acute perforated
- 2 Recurrent hemorrhagic
- 3 Chronic recurrent (with duodenitis—multiple serpiginous ulceration)
- 4 Obstructive
- 5 Multiple ulcerative (severe symptoms, short duration, no relief by medical regimen)

6 Chronic perforative (with attachment to pancreas or gall-bladder)
Case reports illustrative of those several types have been made previously by Thompson²⁵

The perforated duodenal or gastric ulcer is of course always a surgical emergency Shelley²⁶ reviewed 82 cases in which there was an immediate mortality of 18.3 per cent due to peritonitis and pulmonary complications. His follow-up records of cases were excellent and his statistics confirm the conservative opinion that a single inversion of a perforated ulcer with drainage of the abdomen will save more patients than any other procedure. Adding posterior gastro-enterostomy to the load the patient already carries will in not a few instances be a factor in causing his death. It is only in rare combinations of circumstances favorable to the patient, such as a very recent perforation with actual or impending pyloric obstruction, that gastro-enterostomy should be done simultaneously with inversion. Should obstruction occur later, gastro-enterostomy can be done with minimal risk. Many patients after perforation are strikingly free from symptoms following single inversion. This fact alone condemns the routine performance of gastro-enterostomy in the presence of acute perforation.

The question of closure of such perforated cases without drainage again is a matter of very careful individual judgment and opinion. Closure without a drain in any wound such as a thyroidectomy, radical or simple mastectomy, or cholecystectomy is an ideal which should not be too strenuously pursued. In most cases of perforated duodenal ulcer, or of any other hollow viscus, it would seem advisable to follow the practical old masters who almost invariably drained such cases.

There is no one who will disagree with the statement that obstructing duodenal or pyloric ulcer patients should be treated by appropriate surgical procedure such as gastro-enterostomy, pylorotomy or gastro-duodenostomy. The results obtained by gastro-enterostomy in this type of case have been uniformly satisfactory. It is the duodenal ulcer patient without obstruction who has long been a subject of controversy between internist and surgeon.

It is a very serious mistake and an absolutely unjustifiable policy to deny surgical relief and cure to those unobstructed patients who have chronic or severe acute symptoms unrelieved by an adequate medical regimen. Such patients suffer intensely and should demand surgical treatment if and when they fail to get relief of their symptoms by medical measures such as diet, sedation, alkalies and rest in bed.

TABLE I
Results Following Various Surgical Procedures for Peptic Ulcer

Operation	No of cases	Symptom free	Incomplete relief	Hospital deaths following operation	Per cent operative mortality	Remarks
Gastro enterostomy	87	80	Persistent mild dyspepsia 7	2	2.3	Deaths due to vicious circle and intestinal obstruction
Pyloro-plasty	17	16	Recurrent bleeding 1	0	0	Patient with poor result (bleeding) refused re-operation
Bilroth I pyloroplasty	5	5	0	0	0	All patients entirely free of symptoms
Closure of perforation and drainage	20	12	3	2	10	Deaths from peritonitis due to delayed operation
Excision of jejunal ulcer	1	1				Followed gastro-enterostomy done elsewhere in presence of acute perforation
Gastric resection	18	16	Complain of peristaltic rushes 2	1	9.2	Eight patients proved to have malignant ulcer
Total cases	148	Approximately 90% complete symptomatic relief 130	Approximately 10% incomplete relief or poor results 13	5	3.1	Average per cent operative mortality

The severe burning pain which is unrelieved may be a precursor to perforation which will demand emergency surgery under adverse circumstances at great risk. Many duodenal ulcer patients will present themselves with hyper-motility, hyper-peristalsis, severe pain and pylorospasm. These persistent symptoms will frequently require surgical relief after medical failure.

The choice of operative procedure in such patients is of great importance. Some type of pyloroplasty can frequently be used to advantage. This operation is more physiological in that it empties the acid gastric contents into an area of high alkalinity which is biologically designed to receive them. The fearful complications of gastro-jejunal ulcer are avoided. It is, however, not always technically possible to perform pyloroplasty or pylorotomy with minimal risk. Gastro-enterostomy when properly performed will give symptomatic relief to the majority of such patients who suffer from chronic (non-obstructive) single or multiple ulceration of the duodenal mucosa.

The term "complicated duodenal ulcer" has been frequently used to designate those cases which do not obtain relief by medical regimen. This terminology is acceptable, but one cannot accept the viewpoint that a patient without organic obstruction or gastric motor insufficiency is to be advised against surgical treatment. Such advice is bad and can only be accounted for by a misconception of the pathologic changes in the duodenum which accompany peptic ulceration.

Peptic ulcer of the gastric mucosa should always be considered potentially malignant. The majority of benign gastric ulcers quickly heal under a careful dietetic and sedative regimen. Occasionally a stubborn case will require hospitalization and jejunal feedings by the Levin trans-nasal duodeno-jejunal catheter. In the event that an immediate response to treatment does not result, then all gastric ulcers no matter what their size or location should receive the benefit of surgical exploration. Total gastrectomy, while a formidable procedure carrying a relatively very high mortality rate, has been successfully performed many times by competent gastric surgeons. Gastric cancer even when viewed through rose colored glasses is still a very grim spectacle. While extensive resections are possible, recurrences are frequent and permanent cures are few. These facts should not deter one from advising surgical exploration of all suspicious gastric ulcers.

The postoperative management of gastro-duodenal surgical patients is made much easier by the routine use of the Levin nasal catheter with continuous suction siphonage. This method is far superior to the intermittent gastric lavage by means of the large caliber tube. One can determine just when the gastrointestinal tract begins to function. The patient's stomach is never allowed to fill with secretions or liquids, and gastric dilatation is prevented. Nausea and vomiting are almost entirely eliminated by intelligent use of this method which we have employed since 1928. Routine administration of carbon-dioxide inhalations aids in preventing postoperative pulmonary atelectasis. The diet is increased gradually about in accord with the methods employed in the treatment of acute medical cases. Following surgical dismissal all patients are carefully followed up by the clinician who strongly warns them against dietary indiscretion.

These patients can eat a liberal variety of foods but must not be permitted utterly to disregard the knowledge that their gastro-duodenal physiology is not perfect or they would not have developed peptic ulcer, therefore, they

must use caution in their gastronomic behavior following surgical procedures

The teeth, tonsils, paranasal sinuses, cervix, prostate gland are all to be considered possible sources of focal infection and such infections should be eliminated by appropriate methods if found to be present. These patients should always be considered as possessors of physiologically abnormal gastrointestinal tracts and warned to temper their habits with discretion

SUMMARY AND CONCLUSIONS

1 The best interests of the peptic ulcer patient are served by combined medical and surgical judgment

2 The superiority of the trans-nasal suction siphonage in the treatment of gastro-duodenal hemorrhage is emphasized

3 A series of surgically treated peptic ulcer cases is reported in tabular form

4 A very careful postoperative dietary and hygienic regimen is essential in securing permanently good results

REFERENCES

- 1 WALTERS, W, and SNELL, A M Peptic ulcer as seen in central Europe, Proc Staff Meeting, Mayo Clinic, vi, 380-384
- 2 MANN, F C, and WILLIAMSON, C S Experimental production of peptic ulcer, Ann Surg, 1923, lxxvii, 409-422
- 3 BOLLMAN, J L, and MANN, F C Experimental production of gastric ulcer, Proc Staff Meeting, Mayo Clinic, 1935, x, 510-512
- 4 VON WAGONER, F H, and CHURCHILL, T P Production of gastric and duodenal ulcers in experimental cinchophen poisoning of dogs, Arch Path, 1932, xiv, 860-869
- 5 MANN, F C Hodgen Lecture, St Louis Surgical Society, 1933, Bull St Louis Med Soc, xxvii, 221
- 6 McCARTY, W C, and WILSON, L B The pathologic relationship between ulcer and gastric carcinoma, Trans Assoc Am Phys, 1909, xlix, 593-602
- 7 ALVAREZ, W C, and McCARTY, W C Size of resected gastric ulcers and gastric carcinoma, Trans Am Gastro-Enterol Assoc, 1929, xlii, 66-85
- 8 HARGIS, E H, and ROBERTSON, H E Duodenal ulcer, anatomic study, Med Clin N Am, 1925, viii, 1065-1092
- 9 MARRIOTT, W McK An experimental study of the use of unsweetened evaporated milk for the preparation of infant feeding formulas, Arch Pediat, 1929, xvi, 136
- 10 ROSENOW, E C Institutional outbreak of poliomyelitis apparently due to a streptococcus in milk, Jr Infect Dis, 1932, i, 377
- 11 ROSENOW, E C, ROSENDAAL, H M, and THORSNESS, E T Acute poliomyelitis, studies of streptococci isolated from throats and raw milk in relation to one epidemic, Jr Pediat, 1933, xi, 568
- 12 SAUNDERS, E W Infection in gastric and duodenal ulcer, Am Jr Med Sci, 1934, clxxvii, 743
- 13 ROSS, J B The treatment of peptic ulcers with an evaporated milk diet, Ill Med Jr, 1933, lxiix
- 14 SOPER, H W Milk, Am Jr Digest Dis and Nutr, 1935, ii, 113-116
- 15 BALFOUR, D C Perforating ulcer on posterior wall of stomach, Surg Clin N Am, 1931, vi, 735-742
- 16 SOPER, H W The treatment of hematemesis by the retention catheter, Jr Am Med Assoc, 1931, xvi, 771-774

- 17 BALFOUR, D C Management of lesions of stomach and duodenum complicated by hemorrhage, Jr Am Med Assoc, 1927, lxxvii, 1656
- 18 BEVAN, A D Hemorrhage from the stomach, Surg, Gynec and Obst, 1924, xxxviii 358-360
- 19 LAHEY, F H Treatment of gastric and duodenal ulcer, Jr Am Med Assoc, 1930, xev, 313
- 20 WARD, R An apparatus for continuous gastric or duodenal lavage, Jr Am Med Assoc, 1925, lxxiv, 1114
- 21 WANGENSTEIN, O H, and PANE, J R Nasal catheter suction siphonage, its use and technique of its employment, Minn Med, 1933, x, 96
- 22 ORR, T G, and CURPHY, W C Pre-operative preparation of the dilated stomach Surg, Gynec and Obst, 1934, lx, 92-93
- 23 KLEIN, E, ASCHNER, P W, and CROHN, B B The end-results of partial gastrectomy for primary gastric and duodenal ulcers, Trans Am Gastro-Enterol Assoc, 1933, 197-205
- 24 WALTERS, W The problem of gastric resection for duodenal ulcer (Editorials), Surg, Gynec and Obst, 1935, lx, 267
- 25 THOMPSON, J W Duodenal ulcer, surgical treatment, Jr Mo St Med Assoc, 1930, 582-584
- 26 SHIFLEY, H J Perforated peptic ulcer, Am Jr Surg, 1932, xv, 277-303

OBSERVATIONS ON THE EFFECT OF SUDDEN CHANGES IN ARTERIAL TENSION IN ANGINA PECTORIS*

By E W BITZER, M D , F A C P , *Tampa, Florida*

ANGINA pectoris is generally considered to be a manifestation of diseased coronary arteries. Coronary sclerosis is present in most cases but not in all, and marked coronary sclerosis may be found in cases which have not shown the anginal syndrome. To account for the cases with little or no pathological findings the theory of coronary spasm has been advanced^{1, 2, 3}. This is also a possible explanation of the angina of rest. The finding of changes in the R-T segment of electrocardiograms taken during spontaneous or induced attacks^{4, 5, 6} has been considered confirmatory evidence of the occurrence of coronary spasms. It is known, however, that changes in the R-T segment may occur in coronary thrombosis without pain. Similar changes have been produced by exercise in patients with angina pectoris, without precipitating an attack of pain⁶. Such changes have also been reported in rupture of the right auricle⁷ and have been produced experimentally by injecting various substances into the pericardium⁸.

It has been found that the coronary constrictor mechanism is poorly developed in animals,^{9, 10} and the suggestion has been made that a failure of the dilator mechanism may account for some cases of angina pectoris. Wenckebach¹¹ believes a failure of the depressor mechanism is responsible for a sudden increase in aortic pressure and that this is the mechanism of attacks in certain cases which he designates true angina pectoris, as distinguished from coronary sclerosis.

The nerve control of the coronary circulation has not been definitely worked out. The vagus is probably the coronary constrictor and the sympathetic the coronary dilator¹². The reverse is true in the peripheral vascular system. Drugs that constrict the peripheral vascular system frequently precipitate attacks of angina pectoris, and dilator drugs usually relieve the pain. These drugs may act through a local effect on the blood vessels rather than through the nerve mechanism.

The purpose of this study was to demonstrate a possible change in the coronary circulation by a physical stimulus to the vascular system that did not entail any physical effort and that was free from any local effect on the coronary vessels. The "Cold Pressor Test" of Hines and Brown¹³ admirably fulfills these requirements. It produces in most instances a marked vaso-constriction demonstrable by an elevation in blood pressure. This is usually accompanied by a slight increase in the pulse rate, which suggests a widespread effect on the sympathetic system. If coronary spasm is a factor in producing attacks of angina pectoris, it is an abnormal reaction due to an

* Received for publication May 22, 1935

irritability of the vascular system in the heart. Consequently it seemed reasonable to suppose that in some cases attacks would follow the application of this test.

METHOD

A modification of the cold pressor test was used. The left hand was immersed in a large basin of water at a temperature of 6° C and was kept in the water until the test was completed. The blood pressure was taken on the right arm at least 14 times. A cardiogram was taken immediately before and at the height of the blood pressure reaction. Only one lead was taken during the test and in most instances this was a chest lead with one electrode on the anterior chest, just inside the apex, and the other on the left leg. The subject was questioned before and after the test in reference to pain in the chest.

MATERIAL

Sixty-four patients with angina pectoris were subjected to this test. There were 46 males and 18 females. Thirty-two cases had normal blood pressure, 27 were hypertensives and five were hypotensives. All 64 cases had angina of effort. Ten had both angina of effort and rest. Five conformed to Wenckebach's description of true angina. Seventeen cases had definite histories of coronary thrombosis. The following table gives the age of the patients and the duration of the disease.

TABLE I
Angina Pectoris Duration of the Disease, and Age of the Patients

DURATION	1 yr or less	1 to 3 yrs	3 to 5 yrs	5 to 8 yrs	10 yrs or over
No of Cases	28	14	10	9	3
AGE	30 to 39 yrs	40 to 49 yrs	50 to 59 yrs	60 to 69 yrs	70 to 79 yrs
No of Cases	1	6	24	26	7

RESULTS

Figures 1, 2 and 3 show maximal systolic and diastolic blood pressure reactions to the cold pressor test of the entire group. There was comparatively little difference between the reactions of the anginal patients with normal blood pressure and the hypertensives. The maximal reaction in the hypertensive group was 82 mm systolic and 45 mm diastolic. The maximal reaction in the anginal cases with normal blood pressure was 74 mm systolic and 40 mm diastolic. Fifty-three per cent of the angina pectoris cases with normal blood pressure had a "ceiling" or maximal rise in systolic pressure of 150 mm or more. The average rise in this group was 29.84 mm systolic and 16.53 mm diastolic. A group of 41 cases with normal blood pressure were subjected to the same test. This group was composed of normal in-

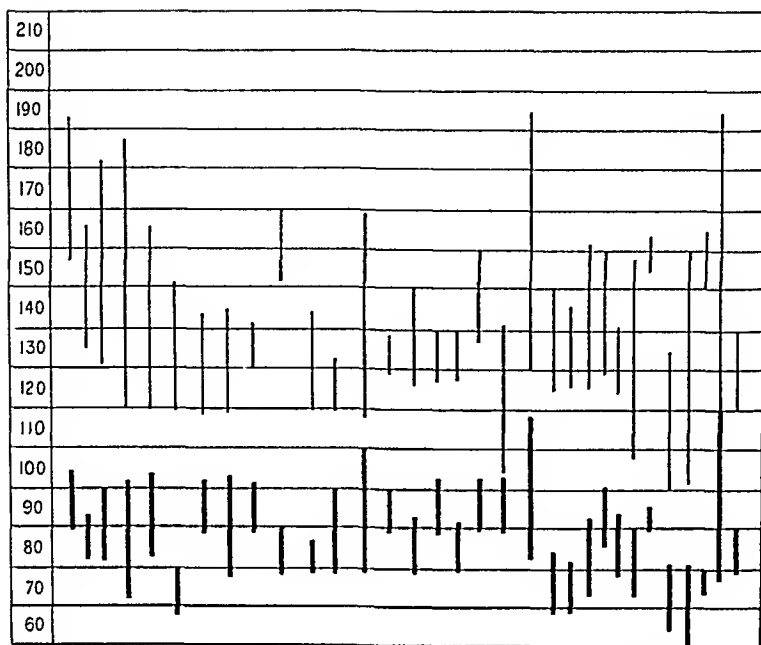


FIG 1 The maximal systolic and diastolic changes in blood pressure during the cold pressor test in 32 angina pectoris cases with normal blood pressure (Heavy lines denote diastolic pressure)

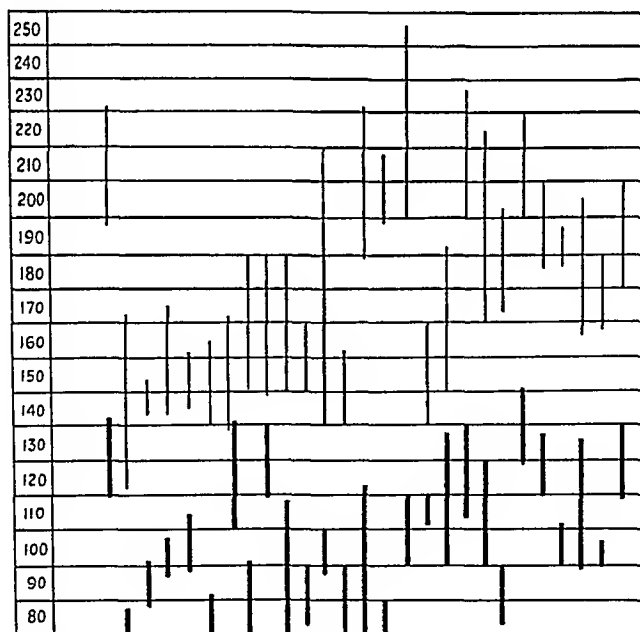


FIG 2 The maximal systolic and diastolic changes in arterial tension during the cold pressor test in 27 hypertensive angina pectoris cases (Heavy lines denote diastolic pressure)

dividuals, cases with cardiac neuroses and cardiac diseases, other than angina pectoris. Fifty-three per cent showed a "ceiling" of 150 mm or above. The average rise in pressure was 32.63 mm systolic and 18.29 mm diastolic. It is possible that some cases in both groups have had hypertension in the

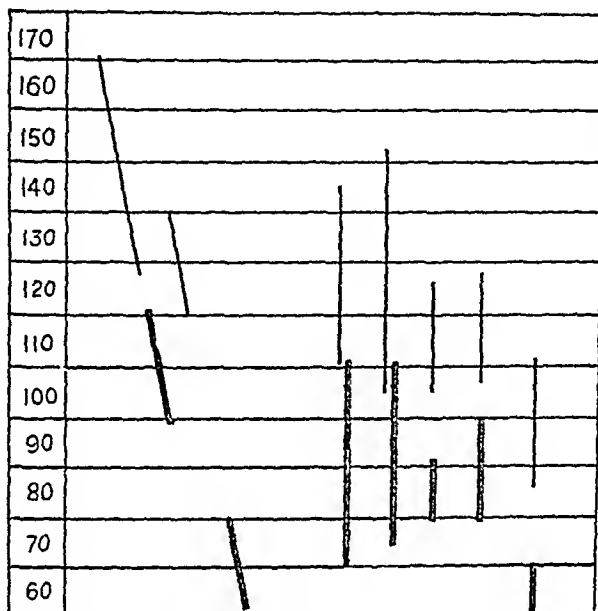


FIG 3 The first four lines (slanting) represent the drop in pressure in two cases of angina pectoris that had a reverse reaction. The other 10 lines (straight) represent the increase in pressure in five hypotensive angina pectoris cases. (Heavy lines denote diastolic pressure.)

past, but it was impossible to prove it. There were two cases shown in figure 3 that had a reverse reaction, a precipitate drop in blood pressure, with a slowing of the pulse rate, pallor and sweating about the face and head.

ELECTROCARDIOGRAPHIC FINDINGS

Sixty-two cases that did not have anginal symptoms were used as controls. There were 10 hypertensive cases. Nine averaged a rise of 39.2 mm systolic and 14 mm diastolic. One hypertensive case showed a reverse reaction, with a drop in pressure from 170 mm systolic and 110 mm diastolic to 118 mm systolic and 85 mm diastolic. The average rise in 41 cases with normal blood pressure was 32.63 mm systolic and 18.29 mm diastolic. Eleven cases with low blood pressure averaged a rise of 24.81 mm systolic and 13.81 mm diastolic.

In this group the changes in the Q, R and T were slight, one mm or less. There were no changes in the R-T segment. In the 64 angina pectoris cases only 12 showed more than 1 mm change in the Q, R, S and T deflections during the cold pressor test. One of these cases showed a reverse reaction, with a drop in blood pressure of 38 mm systolic and 20 mm

diastolic The remaining 11 averaged an increase of 39.3 mm systolic and 15.4 diastolic

There is nothing characteristic in the changes in the Q, R, S and T's in these cardiograms. Such well-marked changes, however, did not occur in any of the other angina pectoris cases or controls. The changes in the R-T

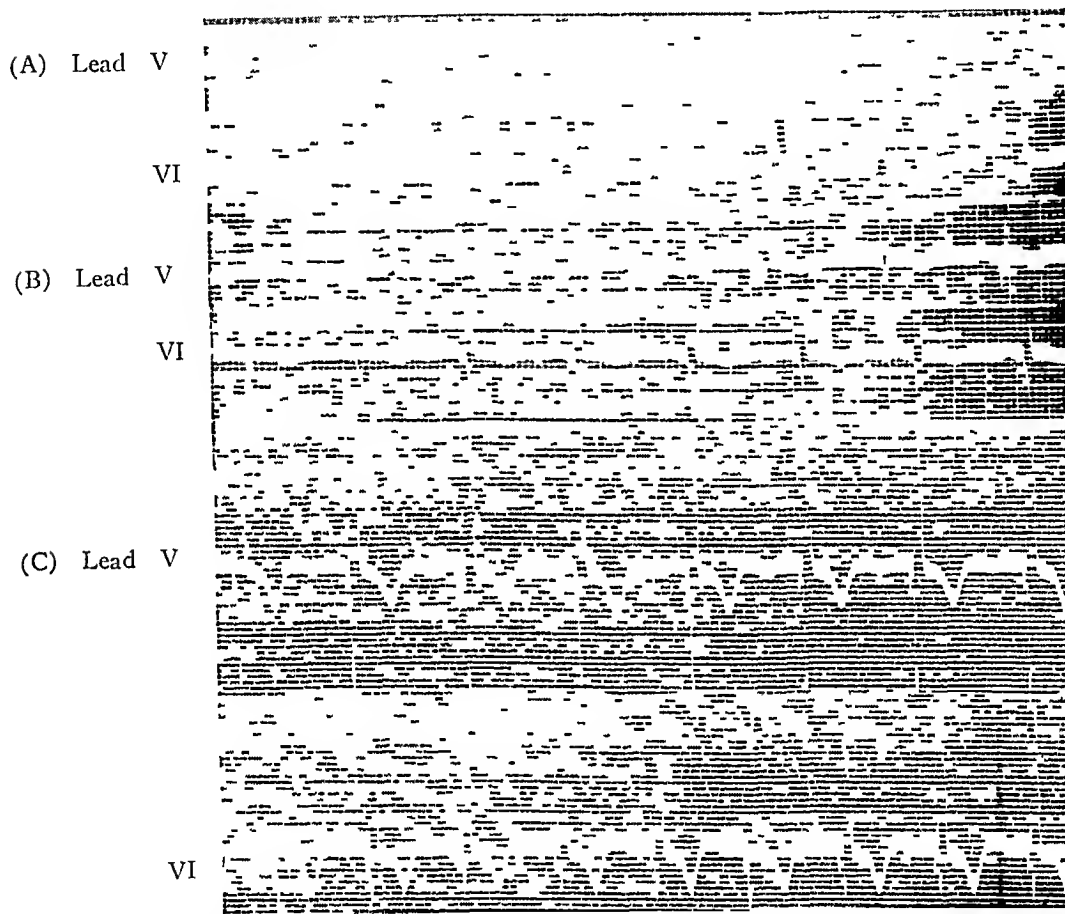


FIG. 4. The first cardiogram in each group is a chest lead (anterior chest, just inside the apex, and the left leg) taken immediately before immersion of the left hand in ice-water. The second is the same lead taken at the high point in the blood pressure. (A) Shows an S which is decreased during the ice-water test. The increase in blood pressure was 4 mm systolic and 5 mm diastolic. (B) Shows an increase in the Q and a decrease in the R during the test. This is a case with normal blood pressure. The increase in pressure was 33 mm systolic and 25 mm diastolic. (C) Shows a decrease in the Q. There is an increase in the notching and in the negativity of the R-T segment. The T is increased. This is a case of malignant hypertension with an angina pectoris syndrome. The increase in blood pressure was 66 mm systolic and 20 mm diastolic.

segment in figure 5 (a) and (b) are of the type suggestive of coronary obstruction. In figure 5 (c) the R-T segment changes from negative to isoelectric during the cold pressor test. Only four cases showed changes in the R-T segment. It seems probable that these changes are significant of a

damaged myocardium It is not possible to assume that they are the result of coronary spasm

PAIN

Only 11 cases failed to complain of pain in the hand immersed Two stated that the pain radiated up the left arm as far as the shoulder Two developed slight shortness of breath and the feeling of oppression in the chest Three cases that had slight anginal pain in the substernal region before the test were relieved when the hand was immersed in the ice water

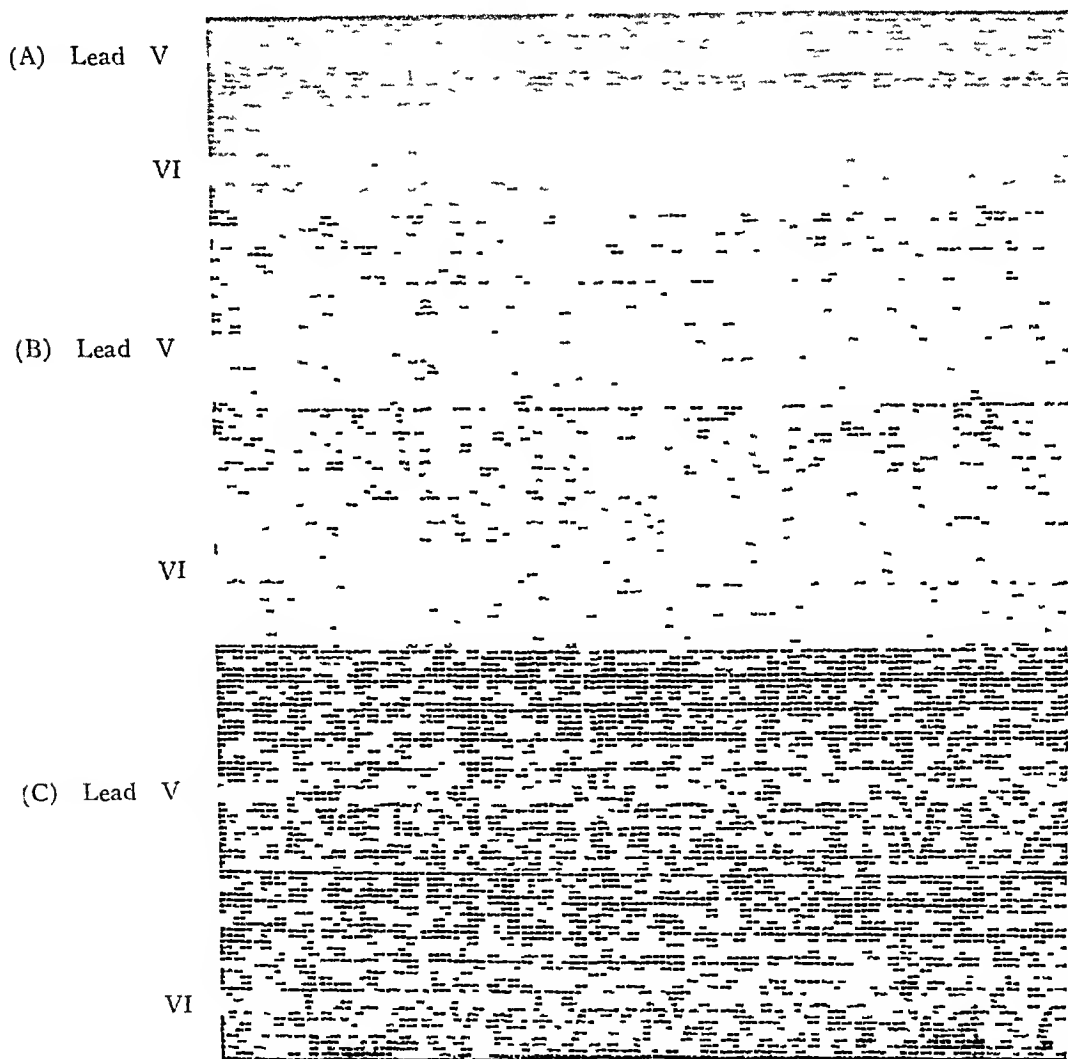


FIG 5 (A) During the ice-water test the R-T interval becomes positive This individual is a diabetic with angina pectoris and a normal blood pressure The increase was 48 mm systolic and 30 mm diastolic (B) A female with hypertension showed an increase in the systolic pressure of 30 mm and 10 mm in the diastolic (C) A hypertensive case The R is increased, the Q and T are decreased and the R-T segment becomes isoelectric The blood pressure increase was 50 mm systolic and 25 mm diastolic

Two developed a pulsus alternans during the test. Four cases showed frequent premature beats that were not present before the test. One case developed a typical attack that gradually subsided when the hand was removed from the water. The pain was in the substernal region and radiated to the back and both arms. The increase in blood pressure during the cold pressor test in this case was 35 mm systolic and 25 mm diastolic. The cardiogram which was taken during the attack failed to show any change in the complexes or in the R-T segment. At a later date the carbon dioxide test was used on this case with an increase in blood pressure from 204 mm systolic and 120 mm diastolic to 240 mm systolic and 150 mm diastolic. This failed to induce an attack.

CASE REPORT

A married woman, 57 years of age, of normal appearance, had lived in Florida for the past 20 years. The family history was negative. There were no known hypertensive cases in the family. She had pleurisy two years ago and malaria one year ago. She stated that her blood pressure was elevated two years ago but did not know how long it had been elevated.

Her chief complaint was pain in the substernal region, radiating to both arms and to the back, precipitated by exercise, excitement or contact with anything cold, relieved by immersing the hands in hot water and by nitroglycerine. She first noticed these symptoms five years ago. Handling ice, eating ice cream, drinking ice water, even standing in front of the open door of an electric refrigerator will precipitate the pain. She discovered a year ago, while washing dishes, that hot water relieved the pain and since then has been immersing the hands in hot water for immediate relief. For the past year walking one-half to two blocks has produced pain in the calves of both legs, which is relieved by standing still for a few minutes.

Examination She was five feet tall and weighed 130 pounds. The teeth, throat, neck, thyroid and sinuses were negative. The reflexes were normal. The skin was normal. The temperature, pulse rate and respirations were normal. The blood pressure was 225 mm systolic and 135 mm diastolic, sitting, 230 mm systolic and 140 mm diastolic, lying, 192 mm systolic and 125 mm diastolic, standing, and 208 mm systolic and 130 mm diastolic, after 50 steps. The radial arteries were palpable, grade one. The retinal arteries showed the early changes of hypertension. Pulsation was not felt in the dorsalis pedis and posterior tibial arteries of either foot. The urine was negative. The abdomen and chest were normal. The heart was slightly enlarged to the left and the substernal dullness of the second space was increased. No abnormal sounds were heard, except an accentuation of the aortic second.

Frequent observations over a period of eight months showed a variable blood pressure ranging from 170 mm systolic and 110 mm diastolic to 225 mm systolic and 135 mm diastolic. On restricted activities and theobromine she has passed a whole month without pain in the chest. During the cold weather this winter, however, she had anginal pain at frequent intervals. Two electrocardiograms, made six months apart, failed to show any abnormalities or change in the complexes.

COMMENT

In the 64 cases studied it is apparent that sudden changes in blood pressure, either a rise or a drop, of short duration and without muscular effort, failed to precipitate attacks of pain. The three cases that had pain in the

chest which was relieved by the cold water suggest an improved coronary circulation, either through the increased blood pressure, or, possibly dilation of the coronaries. However, the pain in the hand while in the cold water may have over-shadowed the mild substernal distress.

The explanation of the cardiographic changes is not so apparent. The Q, R, S and T changes probably have no specific bearing on this problem, though they were not found in other types of heart disease. Of the four cases showing changes in the R-T segment two were suggestive of coronary occlusion. In one of these a similar change was not produced at a second examination. It seems unlikely, however, that this change was the result of coronary spasm since there was no pain, though the criterion of pain is not decisive. The most plausible explanation is the effect of the increased pressure on a diseased myocardium.

In the case that developed an attack during the test, it is apparent that the elevation in blood pressure was not the precipitating factor. Total absence of electrocardiographic changes suggests that coronary spasm did not occur but is not definite proof. In a vasomotor system acutely reactive to cold, it is conceivable that this might reflexly initiate a coronary spasm that failed to show in the cardiogram. The only other possible explanation is that the pain is due to some abnormal condition in the nervous system and is entirely independent of the cardiovascular system.

SUMMARY

1 Sixty-four angina pectoris cases were subjected to the cold pressor test. In one case a typical anginal attack was precipitated by the test.

2 A chest lead was done as nearly as possible at the height of the blood pressure reaction in all 64 cases. Only 12 cases showed well-marked changes in the cardiogram.

3 The failure of extensive peripheral vasoconstriction to initiate attacks of angina pectoris suggests that the cause of such attacks lies in a failure of the vasodilator mechanism rather than in a coronary spasm or in the nervous system.

4 An unusual case is reported in which attacks are precipitated by contact with cold in the absence of physical effort and are not dependent upon changes in arterial tension.

BIBLIOGRAPHY

- 1 LEWIS, T. Pain in muscle ischemia, *Arch Int Med*, 1933, *xlx*, 713.
- 2 LEARY, T. Coronary spasm as a possible factor in producing sudden death, *Am Heart Jr*, 1935, *x*, 338.
- 3 BRAUN, L. Angina pectoris, *Wien Klin Wchnschr*, 1933, *xl*, 1202.
- 4 BROW, G. R., and HOLMAN, D. V. Electrocardiographic study during a paroxysm of angina pectoris, *Am Heart Jr*, 1933, *ix*, 259.
- 5 DIETRICH, S., and SCHWIEGK, H. Das Schmerzproblem der Angina Pectoris, *Klin Wchnschr*, 1933, *xii*, 135.

- 6 SCHERF, D, and ST GOIDHAMMER Zur Fruhdiagnose der Angina Pectoris mit Hilfe des Elektrokardiogramms, *Ztschr f klin Med*, 1933, cxxiv, 111
- 7 CLOWE, G M, KELLERT, E, and GORHAM, W L Rupture of the right auricle of the heart, *Am Heart Jr*, 1934, ix, 324
- 8 RANGLES, F S, GORHAM, W L, and DRESBACH, M Changes in the R S-T component of the electrocardiogram produced by experimental rupture of the auricle of the dog's heart and by pericardial injections, *Am Heart Jr*, 1934, ix, 333
- 9 GREENE, C W Experimental evidence of reflex control of coronary blood flow, *Proc Staff Meet, Mayo Clinic*, 1933, viii, 569
- 10 HINRICHSSEN, J, and IVY, A C Effect of stimulation of visceral nerves on coronary flow in dogs, *Arch Int Med*, 1933, li, 932
- 11 WENCKEBACH, K F Herz- und Kreislaufinsuffizienz, 1931, Theodor Steinkopff, Dresden and Leipzig
- 12 DANIELOPOLU, D, and MARCOU, I Nouvelles recherches sur les vasomoteurs coronariens, *Jr de Physiol et de Path Gen*, 1933, xxxi, 53
- 13 HINES, E A, and BROWN, G E A standard test for measuring the variability of blood pressure, *ANN INT MED*, 1933, vii, 209

THE PRACTICAL USE OF HOBBIES IN THE PRACTICE OF MEDICINE¹

By JOHN R. HAMILTON, M.D., F.A.C.P., *Nassawadox, Virginia*

It is my purpose in the following pages to discuss those conditions in which hobbies are a rational and necessary method of correction, and to point out that the discovery or development of hobbies for patients suffering from certain types of diseases should be more fully recognized as a definite and distinct type of treatment. Hobbies should be studied in regard to the form used, the type administered, the indications and contraindications, harmful effects, and other points of interest so that the results may be observed and controlled as in any other type of treatment.

First let us establish a definition for the term because it is necessary to have a clear conception of a tool before it becomes usable. The medical dictionary and three encyclopedias to which I had access did not even list the term. In Webster's dictionary it is defined as "a subject or plan to which one is constantly reverting, a favorite and ever recurring subject of discourse, thought, or effort, a topic, theme or the like (considered as) unduly occupying one's attention or interest." Evidently, when that definition was composed, a hobby was ascribed very little worth or even desirability. Since that time the need for some recreation or play in the life of everyone has become more generally recognized. Recently the "Leisure League of America" was organized in order to spread the doctrine of play and assist in the choice of workable hobbies. They have already published three excellent booklets and have outlined a very promising series to follow. The first, "The Care and Feeding of Hobby Horses" by Ernest Elmo Calkins, with an excellent bibliography compiled by Hugh Brotherton, is most informative. With this newer, broader view in mind and with especial regard to its application in medicine, I have with a great deal of temerity constructed the following definition paraphrasing Gaskell's description of the action of the heart muscle. "A hobby is the activity in one's life, either physical, mental or both, which possesses the power of rhythmically creating a stimulus to equalize and balance life and to divert it from the overutilization of its powers towards the securing of food, clothing and protection and the accumulation of worldly goods, it enables the possessor to receive all stimuli with a broader and less fatigued outlook, to respond to these stimuli with more poise and judgment, to convey these stimuli throughout life from activity to activity, and maintains throughout one's life a certain ill-defined condition called tone." This, I hope, pictures more nearly the practical, usable therapeutic agent.

In the practice of medicine there has been a general increasing emphasis

¹Received for publication December 26, 1934 (Presented before the Seaboard Medical Association of Virginia and North Carolina, Kinston, N. C., December 5, 1934.)

on the value of preventive medicine. This has brought about a closer contact with those not already stricken with disease. In the endeavor to maintain uninterrupted, happy, healthful living and promote longevity, the beneficial effect of a well regulated life, without unnecessary worry or undue mental tension and with the proper exercise, rest and fresh air, is worthy of consideration. The accomplishment of such a state could be aided by the development of a suitable hobby and would, I believe, greatly reduce the future number of some diseases such as certain types of psychoneuroses, gastrointestinal tract disorders, and cardiac diseases. And with the public's growing regard for a periodic check-up by a physician, more and more opportunity will be furnished the medical profession for preventive measures. To the knowing eye of the physician many a person is climbing the ladder of success so intently that he sees only the rungs underfoot and will crash to the ground before he realizes that the angle of inclination is too steep for him ever to reach the top. On the other hand the physician also sees the type of patient who has never attempted to climb, bound by the monotony of existence, his life so dull and tedious that he has never even seen the ladder. Both types of patients, the over ambitious and those lacking in ambition, need a hobby as definitely as others need relief from constipation.

Rest, either absolute or at intervals, is an important factor in the successful treatment of many diseases. First there must be rest in the physical sense. In the case of an irrational patient, cessation of motion may be forced by a sufficient number of attendants and a restraining sheet. Except in such cases few would feel the rest obtained was beneficial. Obviously, mental acquiescence is necessary to physical repose. If, passing beyond this stage of mental acquiescence, real mental relaxation can be reached, with the physical being rested because it is dissociated (so to speak), and the mind happily and peacefully occupied, then we have achieved the state of real rest. Here again a hobby is a vital factor in securing desired results.

In diseases such as typhoid fever, streptococcic septicemia, influenza, scarlet fever, acute tonsillitis, acute bronchitis, and acute nephritis, the patient is acutely ill and adequate rest is indispensable. A hobby, at first probably entirely mental, then during convalescence involving both mental and physical activities, is a real therapeutic agent. Pulmonary tuberculosis (post-sanatorium care), chronic cardiac insufficiency, angina pectoris (interval treatment), arthritis, and hysteria may be cited as a panorama of the chronic diseases demanding more prolonged treatment. Securing necessary rest in this group is often a difficult task. The physician's advice should not be filled with "don'ts" which may lead to mental anxiety and physical restlessness. Here, then, skillful guidance is essential. Hobbies to divert mental tension or to replace mental idleness, to increase or decrease activity, can be used as a definite therapeutic measure.

As in any other types of treatment certain fundamental principles can be laid down for guidance in prescribing hobbies.

Above all the choice of a hobby must come from some deep-seated in-

terest within the patient himself. A school teacher, with an interesting and colorful exhibit at the end of the term in mind, was greatly disappointed in the following choices of her pupils: cigar bands, movie stars' pictures, marbles, match boxes, and hat bands with slang expressions. But, since they were, for some obscure but real reason in each case, that pupil's genuine choice, substitution would have been an error. This illustration from the schoolroom, showing children's natural selection of hobbies in the purest form, also brings out clearly that hobbies are personal interests and not mere fads, not things done to be keeping up with the Joneses, not necessarily beneficial in a commercial sense, and things that cannot stand unskillful handling or too much analyzing.

It is most pertinent that this discussion be illustrated by the hobbies of childhood and adolescence because many of the hobbies of mature men and women are a continuation of, or a resumption of, some interest acquired in youth. Guidance and helpful aid will help many a person uncover innate desires or fancies and lead to the discovery of "an instinctive something that needs but an inner consciousness of its existence to be fanned into a flame of glowing warmth that will sustain him against the cold realities of life" ¹. Then it will transport the patient out of his tedious routine and be his mitigating shock absorber.

When helping in the choice of a hobby, or when attempting to uncover those deep-seated but long-suppressed interests, it is necessary to study the inherent nature of the person in question. At one stage of our development collecting is a major interest often establishing habits and interests which are retained throughout life. For those there are many and varied choices, from paintings to canning recipes and back through butterflies, Victrola records, autographs, stamps, pieced quilts, post cards, pipes, embroidery stitches, early American bottles, guns, clocks, old maps, stuffed animals, and etchings.

There is a large group of people engaged in some business or profession who yearn to work with tools and their hands. Too often the unfortunate regard of parents for "white collar" jobs has forced a boy with the making of a first class mechanic or cabinet-maker to end his days as an unhappy, third rate bank clerk or insurance collector. On the other hand, others happily and successfully engaged in the bond business or practice of law have a mechanical turn. People of these types may find relaxation in a basement work shop making ship models or doll furniture or reconditioning old furniture. These hobbies would come under the general classification of "making things" ² which includes the arts and crafts, wood-carving, painting with water colors, making marionettes, landscape gardening, carving soap models, crocheting, photography, weaving, making models of airplanes, hooked rugs, building boats, taxidermy, and the like.

Another group of persons is interested in more active pleasures: golf, baseball, polo, racing, walking, coasting, bowling, foxhunting, fruit raising,

bee culture, training dogs, cruising, raising carrier pigeons These would come under the general head of "doing things" ²

At the other extreme are those who like to retire from action and are happiest surrounded by books, engaged in research or some intellectual feat such as translating Dante from the original or following Einstein through the theory of relativity The hobbies for these could come under the general classification of "learning things," ² which would include history of railroads, astronomy, study of birds, chemical experiments, tracing one's ancestors, study of ferns, and following Byrd's expedition to the South Pole

The flexibility of hobbies or the group of allied hobbies centering around most subjects of interest must be kept constantly in mind For example in the case of a patient who is interested in boats there is a wide range of activities enabling one to choose that phase best suited to the case The patient who is confined to his bed or room or who enjoys quieter pursuits may follow stories of the sea, either reading to himself or listening to someone else, or he may collect pictures of various types of boats or ships The man financially unable to buy the materials for a real boat or to take time off from work for long trips may enjoy making ship models The man of means who is interested in boats but unable (either in fact or imagination) to leave his business over long enough periods for sea voyages may find relaxation in a collection of paintings or etchings of ships Another patient may spend long and happy hours tinkering with an antiquated engine in a battered motor boat and never envy his richer neighbor with the perfectly appointed yacht

Fishing, in itself, brings activity of mind and body, fresh air, and change of surroundings When moderate exercise is indicated, the patient can be limited to fishing from the bank of a stream or from a power boat Trout fishing or deep-sea fishing provide more strenuous activity For those for whom actual fishing must be prohibited or who are not within easy reach of a stream or sea-port, there are the collecting of rods and flies, mounting specimens, painting or kodaking fish, making flies, reading books on fishing, and the study of fishing grounds These various phases allow great range in activity, time spent, and financial outlay

It is usually best that a hobby not be too closely related to one's vocation When a bank cashier leaves his work after a day spent indoors with ledgers and figures, a ten-mile drive in search of an antique comb-back, Windsor chair reported seen in a Negro hut, provides fresh air and physical exercise as well as relaxation and stimulation Recently, many of us were startled by the announcement that the King of England knits and crochets scarves and mufflers, but what could be a more restful diversion for one who spends such a large part of each day hurrying from corner stone laying to opening of a hospital speech and constantly in, or rather before a crowd

A hobby should be chosen with regard to the age of the patient and should allow modification as age increases A man who spends his vaca-

tions climbing mountains at the age of thirty in later years will have to content himself with arranging his snap shots in scrap books or following the ventures of others. This may often be provided for by choosing a series of allied hobbies, the more active ones leading into the less strenuous as time passes. On the other hand as age increases leisure time usually increases, and a man or woman who starts a stamp collection early in life may allow more and more time to it as years pass. Thus both the collection and the interest may grow apace until the classification and arrangement of the collection, attending auctions, reading pamphlets, books and catalogs, and comparing notes with other enthusiasts fill with delight what for many is a wretched void.

Of course, one consideration behind every choice is the patient's financial condition. But here again alteration is usually possible. The man with limited means naturally cannot collect old masters. But he can find excellent reproductions well within his means. The woman who is a garden enthusiast may not be able to buy imported bulbs but she can still create a bit of satisfying loveliness with tamed donations from nature.

The physician must not be surprised or discouraged if his patient suddenly loses interest in a hobby he has been following either from choice or at the physician's suggestion. Neither should it be pushed, but dropped, and new interests found in the same way as one would not prescribe quinine for a patient with a known idiosyncrasy to the drug. As in any other procedure which the physician adopts, his interest and skill will increase with continued use.

It has been said that "The knowledge which a man can use is the only knowledge which has life and growth in it and converts itself into practical power. The rest hangs like dust about the brain or drops like rain drops off the stones" (Froude). How often in medicine recurs the advice "Help the patient develop a hobby," or "The patient should find a hobby," but because of the vague conception of the term in the minds of both patient and physician and the lack of practical suggestions this excellent therapeutic measure often fails to "convert itself into practical power." It is hoped that this paper has shown that helping develop a hobby is both practical and simple with only a few general rules and underlying principles to be considered.

REFERENCES

1. TAUSSIG, C. W. and MEYER, T. A. Book of hobbies, Minton, Balch, 1924.
2. CALKINS, E. E. Care and feeding of hobby horses, Leisure League of America, 1934.

CASE REPORTS

PROLIFERATIVE INTIMITIS OF SMALL ARTERIES AND VEINS ASSOCIATED WITH PERIPHERAL NEURITIS, LIVEDO RETICULARIS, AND RECURRING NECROTIC ULCERS OF THE SKIN

By NELSON W BARKER, M D, F A C P, and THOMAS W BAKER, M D,
Rochester, Minnesota

THE various types of occlusive vascular disease produce clinical pictures which may vary greatly with the extent and situation of the lesions and the rapidity with which they develop. However, certain clinical and pathologic entities have been established and although their exact etiology still remains obscure the diagnosis usually is not difficult. This case is presented because of its unusual clinical and pathologic features which do not conform to any of the more common syndromes.

One of the outstanding features of the case was the marked degree of livedo reticularis. This is a descriptive term which has been given to a permanent bluish-red, retiform mottling of the skin of the extremities and frequently the trunk also. According to Williams and Goodman, the basis for livedo reticularis, also called livedo racemosa and generalized telangiectasis, is a capillary dilatation or atony which may be primarily functional or may be associated with congenital vascular anomalies or organic disease of small arteries and veins. In 1893, Unna reported a case in which there were multiple ulcers and "chronic phlebitis". Endarteritis of small arteries and endophlebitis of small veins have been found in the skin at biopsy in cases of livedo reticularis, by Stokes, Urbach, Becker, and Ebert. Periarteritis and periphlebitis also have been noted occasionally. No extensive pathologic studies of larger vessels and nerves have been described.

The etiology of the vascular lesions in various cases, which have been reported, has been ascribed to syphilis (Ehrmann), arteriosclerosis (Giosz and Kerl), and tuberculosis of the erythema induratum type (Williams and Goodman). Stokes, Becker, and Ebert have reported cases in which no etiologic factor was apparent. Associated ulceration of the skin was noted also in Ebert's case. The combination of livedo reticularis, recurrent indolent ulcers, severe intractable pain, and acute arterial occlusion of the toes has not been described.

CASE REPORT

History A man, aged 34 years, formerly a machinist, first came to The Mayo Clinic in October 1932. Eight years before, a diffuse reticulated purplish mottling had gradually developed over all the extremities and to a lesser degree over the trunk.

* Submitted for publication May 13, 1935.

From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

This condition had been more noticeable over the lower extremities than it had been elsewhere, and had been markedly aggravated by cold. A short time after the onset, a series of painful sloughing ulcers had developed on both legs, the usual site had been the lateral aspect of the ankles. The patient said that these ulcers had developed without preceding nodules but always in one of the blue patches. New ulcers never

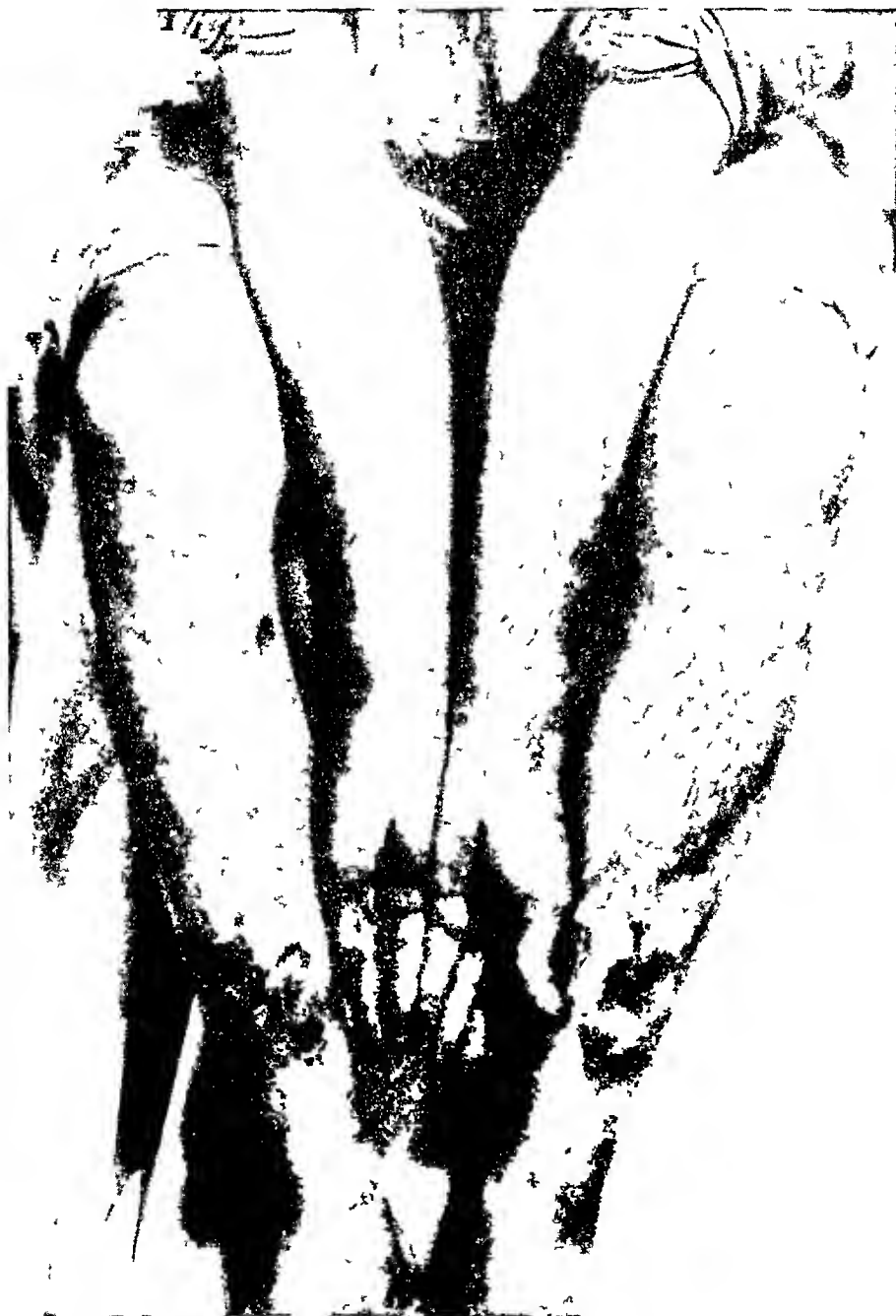


FIG 1 Photograph of patient at the time of the first observation, prior to lumbar sympathetic ganglionectomy. Note the reticulated mottling of the extremities, and ulceration and scarring of both legs.

had appeared simultaneously on both legs. Healing usually had occurred within 14 to 60 days, regardless of the therapy which had been employed, and had left an atrophic pigmented scar. The Wassermann reactions of the blood and spinal fluid had been negative. In 1928, four years after the onset, while he had been working with white lead as a lubricant, a left peroneal palsy had developed. At this time, lead had been found in the stools and urine, and basophilic stippling had been found in the erythrocytes. The foot drop had disappeared spontaneously when contact with lead had been discontinued, and there had not been any recurrence nor had this episode seemed to influence the mottling of the skin or development of ulcers of the legs.

The patient had also been the victim of two severe attacks of influenza, in 1918 and 1927, and in the latter attack he had observed a disappearance of the livedo during the acute febrile course of the disease. Tonsillectomy had been performed in 1928, without benefit. No familial history of vascular or nervous disease was elicited. There was no previous history of thrombophlebitis or varicose veins.

Two weeks prior to his admission to the clinic, the patient had suffered a sudden acute pain in the right great toe which had become pale and cold and had remained so.

Physical Examination and Laboratory Data Physical examination revealed a well nourished, rather mentally depressed man. Aside from the cutaneous manifestations, the general examination did not reveal anything abnormal. There was a marked livedo reticularis of arms, legs, and lower part of the trunk (figure 1), without definite purpura or telangiectasis. A moderately deep ulcer, measuring 3 by 4 cm, with a dirty sloughing base and slightly indurated borders, was present over the lower third of the anterior aspect of the right leg, and there were several depressed pigmented scars of the skin of both ankles and legs. The entire right great toe was pale and cold and showed a few small patches of subcutaneous hemorrhage. Pulsations in both radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial arteries were present and of normal volume. There were no postural color changes in the feet, with the exception of the right first toe, which became very white on elevation and excessively red on dependency. There were no varicosities. Repeated estimations of the blood pressure were normal. The Kolmer modification of the Wassermann reaction of the blood and the Kline, Kahn, and Hinton tests were all negative. The Mantoux test was negative. No changes in the bones or thorax were revealed by roentgenologic examination, and the routine studies of the blood and urine did not disclose any abnormality. No lead was found in the urine. Special studies of blood smears did not demonstrate anything significant. A small specimen was taken from the margin of the ulcer for biopsy, but it showed only moderate fibrosis and a slight degree of nonspecific, inflammatory reaction. A special tissue stain for tubercle bacilli did not reveal the presence of these organisms.

Therapy and Subsequent Course Since there were definite signs of a recent occlusion of the digital arteries of the right first toe, several intravenous injections of typhoid vaccine were administered. These relieved the pain and caused a return of color. There was also some reason for believing that obliterative and vasospastic changes in the arterioles were the basis for both the livedo reticularis and the ulcers. Therefore, with the idea of increasing the blood supply of both toes and ulcer-bearing regions, a bilateral lumbar sympathetic ganglionectomy was performed by Dr. Craig, on October 25, 1932. The ulcer was entirely healed within 15 days after operation. The mottled blue areas became red below the knees and the toes and feet remained warm and dry. No ulcers appeared for four months, the longest remission that the patient had noted since the onset of the disease. However, at the end of that time they did recur, and an acute arterial occlusion of the left great toe developed. This was similar to that previously experienced in the right great toe, although it recovered more rapidly. Cyanosis, mottling, and sensitivity to environmental cold, of the upper extremities increased so that the patient feared that similar ulcers might develop on the hands.

He returned to the Clinic in August 1933, complaining of new ulcers and of pains in the calves of his legs. The peripheral arterial pulsations again were found to be entirely normal. The feet were warm (34°C). The livedo reticularis was the same in the legs as it had been before, but it was more marked in the arms, and the hands were cold and slightly cyanotic. An arteriogram (Allen and Camp technic) of the right arm did not reveal any evidence of arterial occlusion. Sufficient typhoid vaccine to give a systemic fever of 104°F produced an increase of the skin temperatures of the fingers from 28.2°C to 37.9°C .

Three applications of roentgenotherapy to the ulcerated areas of the legs and six subcutaneous injections of an autogenous vaccine, which was prepared from a culture of the ulcer, were administered. Partly at the patient's request, and as a prophylaxis against a possible ulceration of the hands and arms, bilateral cervicothoracic sympathetic ganglionectomy was performed by Dr. Craig on September 9, 1933, with almost complete relief of symptoms and signs in the upper extremities. During the postoperative convalescence, the ulcers of the legs healed but whether we are justified in ascribing this to therapy other than enforced rest in bed is doubtful.

The patient was discharged in October 1933, but returned for further observation in January of the following year. In the interval between visits, he had been free of ulcers for two months, only to have them return with increasingly severe pain which finally required morphine. On his admission to the hospital at this time, a deep sloughing ulcer, which was similar to the previous ones, but larger, was present over the external malleolus of the left ankle. There was also a small area of discoloration of the right calf, which appeared to be about to break down. A biopsy of this lesion revealed some fibrosis of the corium, but did not reveal any inflammatory reaction. In two arterioles in the cutis there was slight hypertrophy of the media. A roentgenologic examination of the bones of the leg showed only a slight osteoporosis. Seven daily intravenous injections of 20 cc of activated sulphur, and six injections of the autogenous vaccine (0.1 to 0.6 cc) were given without benefit. Potassium iodide and mercury were administered by mouth, but there was no change. Hot packs and pantocain ointment were applied locally but gave only slight relief from pain. Following this, five injections of 0.4 gm of neoarsphenamine were administered in three weeks, without noticeable benefit. Wet dressings of potassium permanganate and thioglycerol were employed but no healing followed. The patient was even suspected of producing the ulcers and keeping them from healing, and for this reason, an occlusive dressing, designed so that any tampering could be detected, was applied for two weeks, but the ulcers became larger. A dressing of balsam of Peru and an elastoplast bandage were applied, with a rubber sponge to exert pressure over the ulcer, as advocated by McPheeters and Merkert for the treatment of ulcers, caused by venous stasis, but no appreciable healing resulted, and the pain increased until opiates were again required. The patient became very nervous and mentally depressed, and finally insisted that the left leg be amputated, although he was fully aware that this was no insurance against recurrence of ulcers in the remaining leg. An amputation below the knee was finally performed by Dr. Ghormley, June 28, 1934. Convalescence was uneventful, and the stump healed promptly. The patient returned home in August. He recently has reported that ulceration has recurred in the remaining leg. There has not been any noticeable progression or improvement in the livedo reticularis.

Pathologic Studies Dissection of the anterior and posterior tibial arteries of the left leg, and their vena comites, did not reveal any evidence of occlusion or gross pathologic changes. However, the walls of both the long and short saphenous veins were extremely thick, and the lumina of these veins were very small. Histologic sections of the base and the margins of the ulcer showed

considerable fibrosis of the subcuticular tissue and a mild degree of inflammatory reaction. There was no evidence of any specific type of granulomatous lesion, but there was chronic ischemia with low grade secondary infection of the tissues. Sections of the toes, particularly the first toe, revealed increase in the fibrous



FIG 2 Photomicrograph of section of small artery from base of ulcer, showing active intimal proliferation. Hematoxylin and eosin stain ($\times 215$)

tissue, and decrease in the fat, with atrophy of the cutaneous glands. The essential histologic lesions were found in the blood vessels and nerves. Sections of the large arteries, such as the posterior tibial, showed slight proliferation of the intima only. However, more extensive proliferation of the intima and definite perivascular fibrosis were found in many small arteries and veins (figures 2 and 3). This was particularly true in vessels which were 200 to 1,000 microns in diameter and situated in the tissue in the base and margins of both the active and healed ulcers. These vessels were situated farther below the cutis than were the vessels in the tissue which was removed at biopsy. In some of the arteries of the first toe, the lumen was occluded by a fibrous mass and there was marked periarterial fibrosis, these apparently represented a late stage of the lesion (figure 4). There was little or no inflammatory reaction in either the media or adventitia of the small arteries and veins. The thickening of the walls of the long and short saphenous veins was almost entirely the result of proliferation of the intima and there was little inflammatory reaction in the wall of the

vein itself (figure 5). Many arterioles (25 to 100 microns) had abnormally thick walls and small lumina, in some, there seemed to be hypertrophy of the muscle and slight proliferation of the intima. In many places, these were surrounded by solid fibrous tissue.

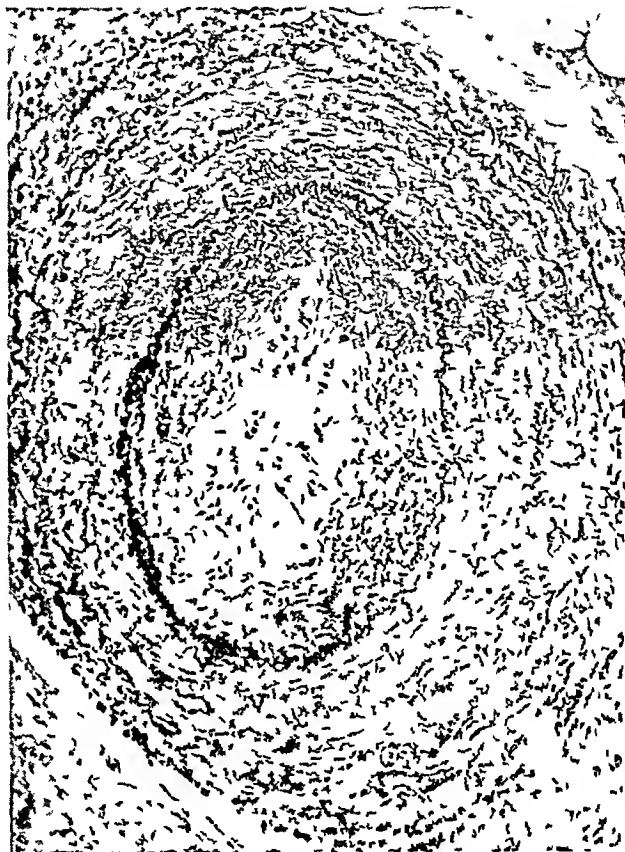


FIG 3 Photomicrograph of section of small vein near base of ulcer, showing well advanced intimal proliferation and almost total occlusion of lumen, stained with elastin H stain ($\times 95$)

The peripheral nerves all showed perineural and intraneural fibrosis and patchy loss of the myelin sheaths. These changes were only of slight degree in the anterior and posterior tibial nerves and their branches, but were very marked in the long saphenous and sural nerves, in which only a very few myelin sheaths in each nerve bundle took the Weigert stain (figure 6). The vasa nervorum showed the same changes noted in other small arterioles and veins.

COMMENT

In summing up the essential clinical features of this case, we have a young man, aged 36 years, who, for 10 years, had had a permanent livedo reticularis of the legs, arms, and lower part of the trunk, and a series of ulcers of the lower legs which gradually had become more and more difficult to heal and gradually had become more and more painful in spite of a wide variety of therapeutic pro-

cedures designed to increase circulation and promote healing. Finally, amputation of the leg was necessary because of pain in a large ulcer which could not be healed. There were two episodes of acute arterial occlusion of toes, without definite gangrene or ulceration. There was no evidence of tuberculosis or syphilis. A lumbar sympathetic ganglionectomy seemed to inhibit the formation of the ulcers for a short time only.



FIG 4 Photomicrograph of section of long saphenous vein, stained with hematoxylin and eosin. There is marked proliferation and fibrosis of intima, but no inflammatory reaction in media ($\times 25$).

The essential pathologic changes appeared to be a proliferative, occlusive intimitis of small blood vessels, both arteries and veins, and of larger superficial veins. The term proliferative intimitis is used because both arteries and veins were affected and endarteritis and endophlebitis are loosely used in medical literature to denote a variety of vascular lesions. The arterial occlusions produced varying degrees of chronic ischemia of skin and toes and a rather marked degree of ischemic neuritis. There was also a definite thickening of the walls of the arterioles, which possibly was secondary. There was some evidence in favor of an additional factor of venous stasis in the production of the ulcers, because of the fact that veins were obstructed as well as arteries. The pathologic picture of the vascular lesions suggests that they were slow in development and dis-

tinctly different from the lesions of thromboangitis obliterans, arteriosclerosis, and periarteritis nodosa

There is no definite clue as to etiology. One would suspect that the proliferative intimitis was a reaction of the vascular endothelium to some chronic toxemia, endogenous or exogenous. There was not any evidence of syphilis, tuberculosis, or other systemic or focal infection. It is noteworthy that the pa-

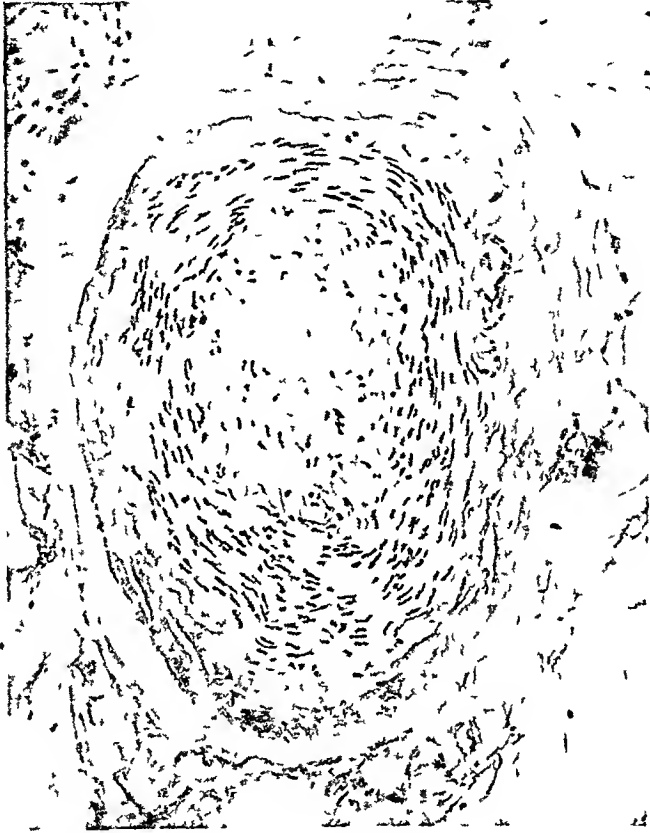


FIG 5 Photomicrograph of section of small artery of first toe, showing complete occlusion by intimal proliferation with secondary hyaline fibrous degeneration, and periarterial fibrosis. Hematoxylin and eosin stain ($\times 155$)

tient had had an episode of clinical lead poisoning four years after the onset of the disease, and it is possible that this contributed to the pathologic changes in both blood vessels and nerves. Whether or not he had had atypical or mild chronic lead poisoning since the onset of the disease is problematical as he had had no known exposure to lead. Subsequently, the condition had been progressive for a long period when he had no contact with lead, none of the typical symptoms of lead poisoning, and had not excreted any lead in the urine. A specific type of vascular lesion produced by lead poisoning has never been adequately described, and possibly does not exist. Certainly, some individuals can have definite clinical lead poisoning without ever having clinical or pathologic evidence of any vascular disease. However, isolated cases of several types of vascular disease have been described in association with definite clinical lead

poisoning, this may be coincidental. The case, described by one of us (Barker) and Brown, as disseminated arteritis of unknown etiology, showed proliferative intimitis of small arteries as well as arteritis and periaarteritis of arterioles. There was some, though inconclusive, evidence for chronic lead poisoning in this case, because lead was found in the urine before death, and in certain tissues at necropsy.



FIG 6 Photomicrograph of section of portion of long saphenous nerve stained with Weigert's myelin sheath stain. Note disorganization of nerve bundles and only a very few myelin sheaths remaining ($\times 150$).

One remarkable aspect of the case herein reported was its slow but definite progression and refractoriness to therapy. On this basis, the prognosis, both as to loss of other limbs and of life, is uncertain.

BIBLIOGRAPHY

- 1 ALLEN, E V, and CAMP, J D. Roentgenography of the arteries of the extremities, *Proc Staff Meetings of Mayo Clinic*, 1932, vii, 657-662.
- 2 BARKER, N W, and BROWN, G E. Progressive disseminated obliterating arteritis of unknown origin, *Med Clin N Am*, 1933, xvi, 1313-1325.
- 3 BECKER, S W. Generalized telangiectasia. A clinical study, with special consideration of etiology and pathology, *Arch Dermat and Syph*, 1926, xiv, 387-426.
- 4 EBERT, M H. Livedo reticularis, *Arch Dermat and Syph*, 1927, xvi, 426-441.

- 5 EHRMANN, S Weitere Mitteilungen über syphilitische Veränderungen der Hautgefäße und die damit zusammenhängenden Phänomene, Arch f Dermat u Syph, 1912, cxiii, 261-268
- 6 GROSZ and KERL In Verhandlungen der Wiener dermatologischen Gesellschaft, Arch f Dermat u Syph, 1921, cxxxvii, 78-79
- 7 MCPHEETERS, H D, and MERKERT, C E Varicose ulcers Treatment with "the rubber sponge or venous heart" and supportive bandage, Surg, Gynec and Obst, 1931, lii, 1164-1169
- 8 STOKES, J Generalized telangiectasia (livedo racemosa), Arch Dermat and Syph, 1922, v, 781
- 9 UNNA, P G Quoted by Williams and Goodman
- 10 URBACH, E Zur Pathogenese der Livedo racemosa, Klin Wchnschr, 1923, ii, 2027-2031
- 11 WILLIAMS, C M, and GOODMAN, H Livedo reticularis, Jr Am Med Assoc, 1925, lxxvi, 955-958

THE BENEFICIAL EFFECT OF THE DEVELOPMENT OF AN ABNORMAL RHYTHM WITH SLOW VENTRICULAR RATE IN CIRCULATORY FAILURE*

By WILLIAM C COOKE, M D, *San Diego, California*

THAT digitalis medication is often of little value in the treatment of circulatory failure in the presence of persistent sinus tachycardia is well recognized. Digitalis frequently does not slow a regularly beating heart. It has been known since Withering's introduction of the use of the drug that patients with auricular fibrillation respond particularly well to digitalis therapy, and it has been stated frequently^{1, 2, 3, 4, 5} that auricular fibrillation in itself is often well tolerated and compatible with satisfactory cardiac function. That patients with circulatory failure may show marked clinical improvement following the development of auricular fibrillation or other abnormal rhythm with a slow ventricular rate has been seldom emphasized or even mentioned in textbooks or articles on cardiac therapy. An exception to this statement is Meakins' recent observation⁶ that improvement "is often seen when a rapid regular rhythm which cannot be controlled gives place to auricular fibrillation which can be controlled by digitalis, or when complete heart block develops in a failing heart reducing the rate to around forty. In both of these instances great improvement in cardiac function may be seen."

The following case history is an example of the apparently beneficial effect on the circulation of the replacement of a rapid regular sinus rhythm by auriculo-ventricular dissociation upon one occasion and by auricular fibrillation later.

CASE REPORT

The patient, a retired merchant, 63 years of age, entered the hospital on February 25, 1933, complaining of shortness of breath upon exertion and at night, at times accompanied by substernal oppression and asthmatic breathing. These symptoms and considerable gaseous indigestion had been present with gradually increasing severity for the preceding six months although the patient had been confined to his home and was taking adequate doses of digitalis. Previous to the development of his present illness he had been well, although he had known for at least eight years that his blood

* Received for publication April 22, 1935

pressure was elevated. He had had a gonorrheal infection at 28 years of age but denied syphilis, he had had an appendectomy at the age of 25. His family history was negative except that his mother died of uremia at 73 years of age.

Physical examination revealed a well nourished man, apprehensive, dyspneic and moderately cyanotic. Orthopnea was marked and at times periods of Cheyne-Stokes breathing were noted. There were some distention and pulsation of the veins of the neck, and a heaving diffuse precordial pulsation. The left border of cardiac dullness was 12 cm from the midsternal line, 3 cm to the left of the midclavicular line. The heart sounds were of poor intensity with a proto-diastolic gallop rhythm at the apex. The heart and pulse rates were 108. The blood pressure was 170 mm of mercury systolic and 110 diastolic in both arms. Moist râles were present at the bases of both lungs. The liver edge extended 3 cm below the costal margin. There was no edema. Other physical findings were normal. The Kahn reaction of the blood was negative. Urinalysis showed a specific gravity of 1.012, a trace of albumin and numerous granular casts. The blood count was normal. The urea content of the blood was 36 mg per 100 c.c. of blood. The electrocardiogram (figure 1) showed a regular

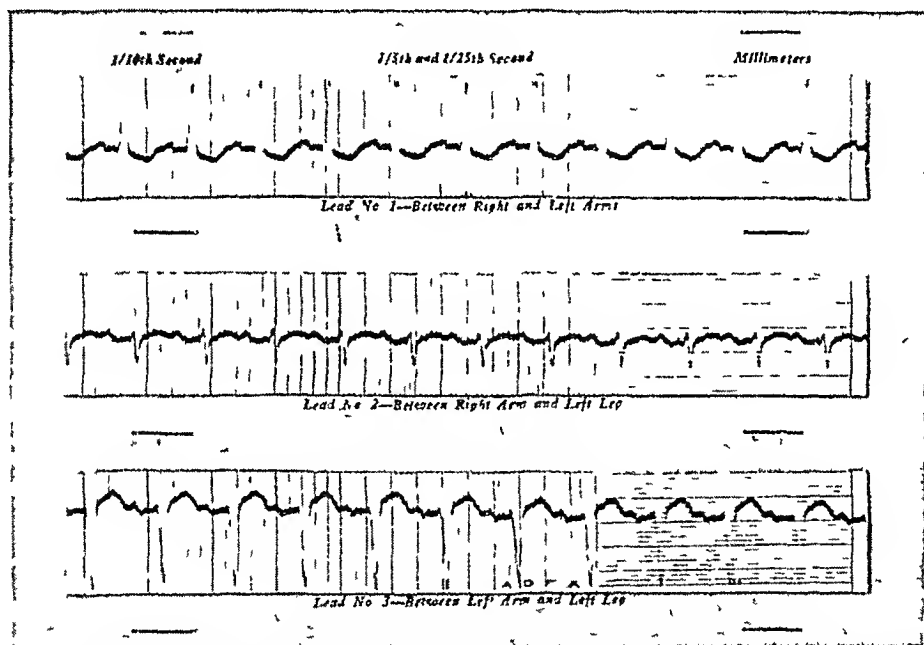


FIG 1 Electrocardiogram taken on February 25, 1933, during first attack of circulatory failure. Regular rhythm, rate 110, P-R interval slightly prolonged (0.22 sec), QRS interval 0.1 sec. Marked left axis deviation. Depression of S-T₁ and elevation of S-T₃, probably due to the marked left axis deviation.

sinus rhythm with a rate of 110, a prolonged auriculo-ventricular conduction time (0.22 sec) and a QRS interval of 0.10 sec. There was marked left axis deviation with depressions of S-T₁, inversion of T₁ and elevation of S-T₃. A diagnosis of hypertensive and coronary heart disease with left ventricular failure was made.

For about one month prior to admission to the hospital the patient had been taking powdered digitalis leaves. He had taken three grains for the first five days and then 1 1/2 grains daily. In view of the prolongation of the auriculo-ventricular conduction time it was felt that he was well digitalized and the maintenance dose of 1 1/2 grains daily was continued. Caffein citrate was given every four hours by mouth and was replaced later by caffein sodium benzoate, grains 3 3/4 hypodermically, be-

cause of nausea Dilaudid, grains 1/32, or morphine sulphate, grains 1/6, was given as necessary to control nocturnal dyspnea and cardiac asthma

During the first nine days of his hospital stay there was little change in his condition except that he became less dyspneic and the Cheyne-Stokes breathing disappeared while under the influence of caffeine The heart rate continued to be rapid, varying from 90 to 130 There was no significant change in the blood pressure readings On March 4, because of the development of nausea and vomiting, digitalis was discontinued It was started again 10 days later with the same dosage of 1 1/2 grains of the leaves daily, but after six days it was discontinued again because of nausea, although the pulse rate was not slowed He still had severe dyspnea and cardiac asthma at night Three days later the administration of digalen, 1 c c three times daily, was started, after six days the dose was decreased to 1 c c twice daily

Three days later, on April 3, the pulse rate became very slow and irregular The electrocardiogram (figure 2 A) showed a shift in the auricular pacemaker and dissociation of the auricles and ventricles with a slower auricular rate The auricular rate was 48 and the ventricular rate 66 Occasionally there was a ventricular re-

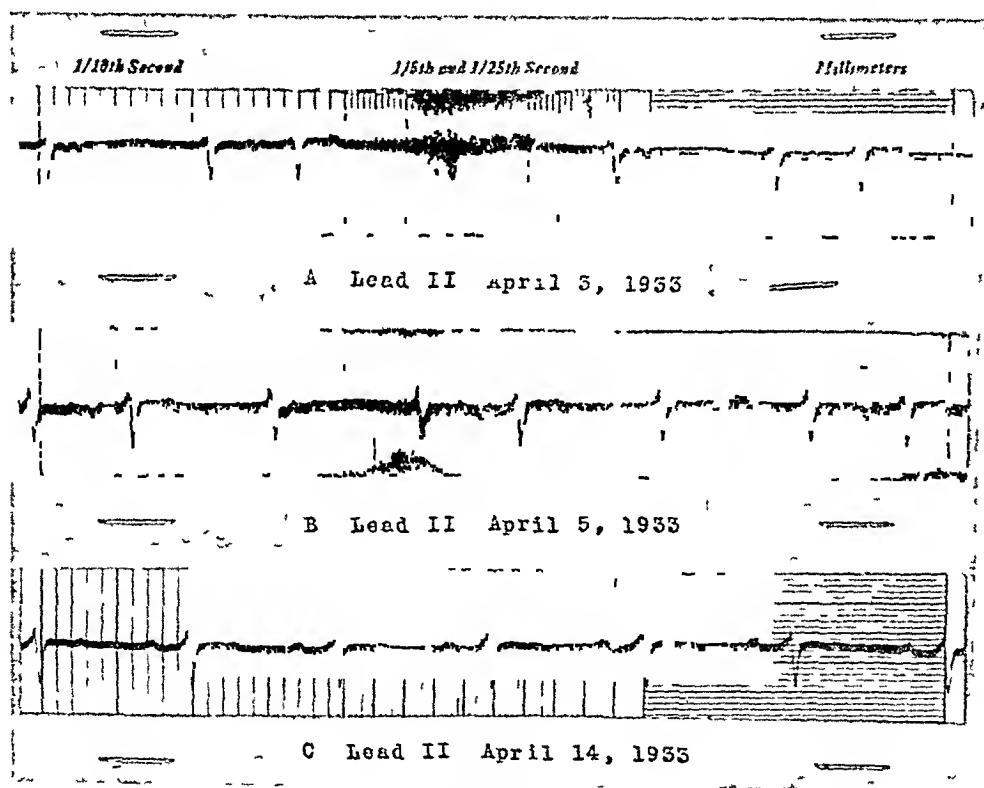


FIG 2 Lead II only of electrocardiograms showing A-V dissociation and return to normal rhythm

A Taken April 3, 1933 Auricular rate 48, ventricular rate 66 P-R interval 0.28 sec The auricles and ventricles are dissociated except periodically when an impulse from the more slowly beating auricle reaches the ventricle during a non-refractory period and causes a ventricular contraction The P-waves are inverted showing a shift in the auricular pacemaker away from the sino-auricular node

B Taken April 5, 1933, one-half hour after the hypodermic administration of atropine sulphate grs 1/100 Shows the same phenomena as (A) except that the ventricular rate is more rapid (80 per min) and the P-R interval less prolonged (0.24 sec)

C Taken April 14, 1933 Regular rhythm, rate 60, P upright, P-R interval 0.28 sec

sponse to the auricular impulse. This occurred when the impulse reached the ventricle during a phase in the cycle in which the muscle was not refractory from a previous contraction. The following day another electrocardiogram (figure 2 B), taken one-half hour after the hypodermic administration of atropine sulphate, grains 1/100, showed the same abnormal rhythm but with less prolongation of the P-R interval (0.24 sec) and a more rapid ventricular rate (72 min). The abnormal rhythm shown in these electrocardiograms is an example of the rare condition of auriculo-ventricular dissociation with unidirectional block and a more rapid ventricular rate such as has been reported by White⁷ and Hewlett⁸ in cases of digitalis poisoning. The drug was discontinued.

In spite of the development of this abnormal rhythm there was very marked clinical improvement. The symptoms of dyspnea, cardiac asthma and Cheyne-Stokes breathing were relieved. The pulse continued to be slow and usually irregular until April 6 when it became regular with a rate of from 60 to 80 per minute. The electrocardiogram taken on April 14 (figure 2 C) showed a return to normal rhythm with auricular and ventricular rates of 60, a P-R interval of 0.28 sec, and no change in the deflection of the various complexes.

The patient was discharged from the hospital on April 17 with no symptoms of circulatory failure. He was advised to remain in bed at home and to take digitalis leaves, gr 1 twice daily. For the next two weeks he continued to feel well. At the end of that time his heart rate gradually began to increase. Coincident with this increase in heart rate the symptoms of nocturnal dyspnea, Cheyne-Stokes breathing and cardiac asthma returned.

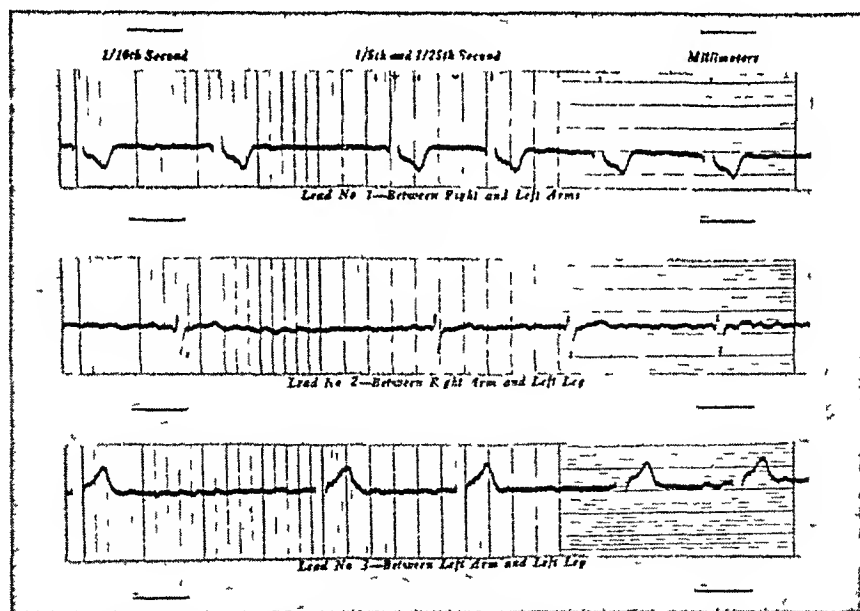


FIG 3 Electrocardiogram taken July 15, 1933, showing auricular fibrillation with a ventricular rate of 40 to 50 per min

He was readmitted to the hospital on May 9 with symptoms of advanced circulatory failure. Distention of the jugular veins, moderate cyanosis and very evident dyspnea were present. The heart rate was 110. Pulsus alternans was present with a systolic blood pressure of from 170 to 180 and a diastolic pressure of 110. Many moist râles were heard at the bases of the lungs. In addition to his previous symptoms he now presented the picture of a failing right ventricle with enlargement of the

liver and subcutaneous edema over the sacrum. Urinalysis showed a moderate cloud of albumin and many hyaline and granular casts.

The administration of powdered digitalis leaves, gr 1 twice daily, was continued and a diuretic regimen instituted consisting of a low fluid intake, ammonium nitrate, grains 90 daily, and the intravenous injection of salyrgan, 1 c.c. at two- to three-day intervals. Under this regimen evidences of congestive failure disappeared in about two weeks' time. However, the subjective symptoms of dyspnea, especially at night, apprehension and occasional attacks of substernal oppression were relieved only partially.

During a period of two weeks his condition remained stationary except for slight recurrences of the congestive symptoms of liver enlargement and dependent edema which cleared up promptly following the administration of ammonium nitrate and salyrgan. The pulse rate remained slightly elevated, varying from 80 to 100 while at rest in bed. There was no significant change in the blood pressure readings.

On July 15, the pulse rate dropped to from 50 to 60 per minute and became irregular. An electrocardiogram (figure 3) showed that the irregularity was now due, not to A-V dissociation, but to auricular fibrillation with a very slow ventricular rate. Coincident with the development of the slow heart rate he began to improve rapidly and in a few days the dyspnea, Cheyne-Stokes breathing and cardiac asthma had disappeared. The administration of digitalis, which was discontinued with the drop in pulse rate, was resumed on July 22 with a dose of 1 1/2 grains daily, and the dose increased to two grains daily about 10 days later. Auricular fibrillation continued with a ventricular rate of from 60 to 70. The patient was allowed to be up for gradually increasing intervals and was discharged from the hospital on August 4 feeling quite well except for weakness and slight dyspnea upon exertion.

It has now been 21 months since he left the hospital. During this time his heart has continued to fibrillate. The ventricular rate has been maintained at from 50 to 60 per minute by the administration of 1 1/2 to 3 grains of powdered digitalis leaves daily. He has felt very well and has had no subjective symptoms of circulatory failure although his activities have been restricted only to a moderate degree.

DISCUSSION

In the case reported, as often happens in the presence of a decompensating heart with a rapid regular sinus rhythm, digitalis administration resulted in very little if any slowing of the heart rate or improvement in the patient's general condition until the development of auriculo-ventricular dissociation with a slow ventricular rate. It was felt that digitalization had been pushed to the limit of tolerance and even intoxication prior to this as nausea and vomiting, necessitating withdrawal of the drug, had developed on two occasions.

The development of an abnormal rhythm was at first considered another unwelcome incident of digitalis intoxication. To our surprise, however, the patient became much more comfortable and began to show rapid improvement as soon as the slow rate developed. Within a period of two weeks his condition was satisfactory for dismissal from the hospital. After the abnormal rhythm had been present for three days the cardiac mechanism again became normal but with a slow rate, and his condition remained satisfactory for a period of two weeks. The rate then increased gradually to from 100 to 110 per minute in spite of continued bed rest and the administration of two grains of digitalis leaves daily. Coincident with the increase in the heart rate, symptoms of circulatory failure again appeared.

When he was admitted to the hospital the second time, moderately severe congestive failure had developed in addition to the marked symptoms of left ventricular failure. The congestive symptoms cleared up promptly following the administration of salyrgan and ammonium nitrate but recurred several times. His improvement was again unsatisfactory until the development of a very slow ventricular rate, this time due to auricular fibrillation with a high degree of auriculo-ventricular block.

Auricular fibrillation has continued for 21 months. The rate has been maintained at from 50 to 60 per minute by digitalis, and there has been no recurrence of circulatory failure although he has been engaging in moderate activity.

The improvement which followed the development of an abnormal rhythm with a slow ventricular rate upon the first occasion was considered a coincidence. A repetition of the experience upon the second occasion convinced us that the abnormal mechanism was really the means by which improvement was effected. The ventricular rate could then be slowed by digitalis and more efficient cardiac function obtained by the increased coronary blood flow and diastolic rest of the myocardium made possible by the longer period of diastole.

CONCLUSION

A case of circulatory failure in which improvement was twice dependent upon the development of an abnormal cardiac rhythm is reported.

Our experience in this case demonstrates the improvement in cardiac function which may result when an abnormal rhythm with a slow rate replaces a regular rhythm with a rapid rate. This improvement may be explained by the more effective depression of auriculo-ventricular conduction by digitalis in the presence of an abnormal mechanism such as auricular fibrillation.

REFERENCES

- 1 WHITE, P. D. Heart disease, 1931, Macmillan Co., New York, p. 651.
- 2 STROUD, W. D., LAPLACE, L. B., and REISINGER, J. A. Etiology, prognosis and treatment of auricular fibrillation, *Am. Jr. Med. Sci.*, 1932, *CLXXXIII*, 48-60.
- 3 WOLFF, L., and WHITE, P. D. Auricular fibrillation, results of 7 years' experience with quinidine sulphate therapy (1921-1928), *Arch. Int. Med.*, 1929, *XLIII*, 653-675.
- 4 NEWMAN, W. W., and SPIRO, H. Quinidine therapy in auricular fibrillation, evaluation based on its use over 6 year period, *Calif. and West. Med.*, 1932, *XXXVII*, 19-25.
- 5 KOHN, C. M., and LEVINE, S. A. An evaluation of use of quinidine sulphate in persistent auricular fibrillation, *ANN. INT. MED.*, 1935, *VIII*, 923-938.
- 6 MEAKINS, J. C. The mechanism of heart failure. (*In* *Modern Concepts of Cardiovascular Disease*, published by The American Heart Association, 1934, *III*, No. 10.)
- 7 WHITE, P. D. Ventricular escape with observations on cases showing a ventricular rate greater than that of the auricles, *Arch. Int. Med.*, 1916, *XLVIII*, 244-249.
- 8 HEWLETT, A. W. Case showing rapid ventricular rhythm with periods of auriculo-ventricular dissociation, *Heart*, 1923, *X*, 9-19.

A REPORT OF IDENTICAL ALBINO TWINS OF NEGRO PARENTS^{*}

By ELMER G WAKEFIELD, M D, *Rochester, Minnesota*, and
SAMUEL C DELLINGER,† *Fayetteville, Arkansas*

THE object of this report is to record identical twins and total albinism occurring in the Negro race. Although such an anomaly in identical twins is exceedingly rare in all races, we believe that the biologic phenomena involved in the production and accidental association of identical twins and albinism have been satisfactorily, if not correctly, explained in the literature on twins, twinning, and albinism. These children were neither pupils nor patients of ours, therefore, the only tests or examinations which could be made were those which are reported here.

The twins were girls, aged about eight and a half years (figure 1). Each weighed 20.9 kg, and was 131 cm in height. They were well developed, well nourished, and appeared healthy. Their hair was abundant, snowy white, and coarse, when combed out, the hair of each child was equal in length. The degree of kinkiness of the hair, the distance between kinks, the hair line on the foreheads, about the ears, along the sides of the temples, and down the back of the necks were identical for each child. The skin, also, was totally devoid of pigment, and there were no freckles, moles, or blotches. The skin was fine and soft in texture, it was moist and delicate. It became sunburned from very short exposure, and required a great deal of protection during the summer months. (One of the children had a large, blistered sunburn on her back at the time of the examination.) The ears were small. The noses were flat, and the nares were wide apart. The lips were moderately thick, and the features were characteristically Negroid. The eyes were squinty, red and nystagmic. When the four eyes rolled from right to left, or vice versa, in order to follow the examining finger, all the nystagmic motions were synchronous. Examination of the ocular fundi revealed that the choroids were devoid of pigment. Examination of the ears, nose, throat, tonsils, thyroid gland, heart, lungs, abdomen, reflexes, and extremities of each child did not reveal anything unusual. After the children had reclined quietly on a bed for 20 minutes, the heart rate of each child was found to be 100 beats per minute. The value for the blood pressure of each child was 130 mm of mercury for the systolic and 70 mm of mercury for the diastolic. Their respirations were abdominal in type, and the respiratory rate was 20 per minute. The following measurements were obtained for each child: circumference of thorax, 55 cm, circumference of neck, 28 cm, circumference of waist, 55 cm, circumference of middle third of thighs, 24 cm, circumference of calves of legs, 20 cm, circumference of middle third of arms, 16 cm, circumference of wrists, 12 cm, length from the fourth thoracic vertebrae to tips of fingers when arms were extended laterally, 70 cm, length of legs from anterior-superior spine of ilium to soles of heels, 65 cm, and length of the middle fingers from wrists, 14 cm.

* From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota, and the Department of Zoology, University of Arkansas, Fayetteville, Arkansas.

† Research Series, number 411.

These children had been born at term, after a short labor which had lasted four or five hours. The second child had been born about 10 or 15 minutes after the first. The mother was certain that there had been only one "after-



FIG 1 The twins at the time they were examined

birth". From birth, the children had been fed on the breast until they had been "two or three" years of age. The mother thought that one of the children always had been a little larger than the other. They had enjoyed good health. Their only illnesses had been measles and chickenpox, which had occurred simul-

taneously and had been of the same severity in each. It had been very noticeable that when one of the children had had a cold or any sort of illness, the other had been affected similarly and to the same degree. Their likes and dislikes of food and clothes were identical. They may have quarrels and disagreements between themselves, however, it is impossible for one of the family to disagree with one of the twins without invoking the anger of the other.

Mental tests under our supervision probably would not have been of much value. These children were quiet, modest, polite and obedient. They had never had an opportunity to go to school. It is our opinion that they were mentally within normal limits.



FIG 2 The maternal grandmother, the mother, the twins, and two of their cousins (girls), two years prior to examination

In neither the father's family nor the mother's family (figure 2) were albinos or admixture of the white race known to be present. The father appeared to be full-blooded Negro. We saw the mother's parents, who, like the mother, were moderately black, and had the characteristic skin, features, and hair of Negroes. The possibility of admixture with the white race or any other race is admitted. This we believe to be irrelevant because albinism and identical twins occur in all races.

COMMENT

The essential feature of albinism is the total absence of pigments of the melanin group, which are the chief factor in the surface coloration among all animals. The absence of these pigments in the eye results in the primary incapacitation of this affliction. The ordinary causes of pigmentation, whatever they may be, are not operative in the albino. Short exposure of albinos to hot sunlight produces a hyperemia which very quickly is followed by the formation of blebs if the exposure is continued. The fat and blood pigments are normal and are excreted in normal quantities in the urine, whereas, the mechanisms for

metabolism and control of the pigments of the melanin group are nonoperative. The foregoing statements apply only to genuine albinism, which is not the most common form observed. In cases of incomplete albinism, the hair has various tints from yellow to red. The usual albinic Negro has yellow hair and pigmented freckles.

There is still a third type which is termed partial albinism. These individuals may have albinic eyes, or they may have albinic skin, normal eyes, white locks of hair. In the latter case, the skin may be flecked with white, and there may be piebald skin or the so-called mosaic inheritance. Clinically, partial albinism should be distinguished from such conditions as vitiligo.

In the majority of instances, albinism continues throughout life. However, it has been stated that an individual who had been born albinic occasionally has recovered. Apropos of this, mention should be made of the seasonal albinism in Arctic mammals and birds. As far south as Minnesota, during winters with much snow, the jackrabbits (subgenus *Macrotolagus*) become albinic.

By selective breeding, albinism can be reproduced indefinitely among lower animals. Thus, the mode of incidence of this inborn error would seem to have a ready explanation, if it is regarded as a rare recessive character in the mendelian sense. If two characters, one of which tends to be dominant, and the other, recessive, are observed in cross-bred individuals, the dominant character will tend to be manifested. This manifestation of the dominant character is explained by the supposition that the germinal cells or gametes of each generation are pure so far as the qualities in question are concerned. It is by such reasoning that Mendel's theory accounts for the numerical results observed by the production of dominant and recessive gametes in equal numbers in successive generations of inbred individuals in the less complicated gametes. The length of life of man, his limited reproductive capacity, his innate tendency to forget unpleasant details in the family history, and especially those matings and the resulting offspring which may be considered undesirable and, finally, his qualities of nomadism, and infidelity, render mendelian interpretation of his dominant and recessive characters practically impossible. Thus, the occurrence of such an inborn error as albinism among human beings is in reality an accidental fertilization of an ovum, which possesses recessive pigmentary characteristics, by a similar spermatozoon, except in consanguineous marriages. To illustrate the results of consanguineous marriages, in 24 families which contained 60 albinic members, five of these latter were the offspring of matings of first cousins. In only two instances was albinism directly transmitted from parent to child.

The reports of genuine identical albinic twins are scarce. According to Garrod,¹ there are 29 records of twins, one or more of whom were albinic. In 11 pairs, both were albinos and in 18 pairs, one twin was normal. In 20 cases the twins were of the same sex, and in seven cases they were of different sexes, the sex of two pairs was not stated. In 10 cases in which both twins were albinic, both of the twins were of the same sex. Since it usually has been argued that identical twins are always of the same sex, probably no more than 10 pairs of these twins were identical. Furthermore, the probabilities are that all of these 10 pairs were not identical twins.

The biology of twins² and the physiology of twinning³ among human beings has been considered in great detail by Newman and his associates. They ex-

pressed the opinion that a single ovum, or identical twins are the result of one of the following processes (1) fission of the blastoderm, (2) double gastrulation, or (3) fission of the bilateral halves of a single embryonic axis. In order for any one of these processes to take place, some retarding mechanism must be present, which prevents normal implantation of the fertilized ovum. One of the following possibilities probably is the retarding mechanism (1) a defective development in the stimulating mechanism of the spermatozoon, (2) a defective stimulating influence of the corpus luteum on the uterine mucosa, or (3) twinning, which is an hereditary character dependent on a recessive gene.

It is interesting that, in a consideration of identical twins who are also albinos, the possibility of both the occurrence of the twins and the albinism may have genetically similar origins. That is, both may be the result of opportunely placed recessive genes so that in the formation of the gamete the conditions are there for both anomalies.

SUMMARY

Identical albino Negro twins have been described. Some of the essential features of albinism and twinning have been discussed. Whatever the fundamental mechanisms are for the production of albinism and twinning, they are present in the original germ plasma. The scarcity of the combination of genuine albinism in identical twins, as indicated by the literature, has been pointed out.

BIBLIOGRAPHY

- 1 GARROD, A. E. *Inborn errors of metabolism*, 1923. H. Frowde and Hodder and Stoughton, London.
- 2 NEWMAN, H. H. *The biology of twins (mammals)*, 1917, University of Chicago Press, Chicago.
- 3 NEWMAN, H. H. *The physiology of twinning*, 1922, University of Chicago Press, Chicago.

EDITORIAL

FACTORS IN THE FALLING DEATH RATE FROM TUBERCULOSIS

FOR fifty years the tuberculosis death rate has shown a striking and fairly steady decrease, so that in the United States it is now about one-sixth of its height in the eighties. Moreover, this remarkable phenomenon has been observed to a greater or lesser extent in most of the European nations. On the other hand a world survey indicates that there are still countries, such as Puerto Rico and the Philippines, in which the mortality from tuberculosis not only stands at a very high level but appears to be actually rising.

The recent studies ^{1, 2, 3, 4} bearing on the causes of these variations have by no means completely clarified the problem, but they have at least broadened our conception of the epidemiology of the disease and incited the collection of more accurate data which will perhaps in time make it possible to substantiate what is at present to a considerable extent surmise.

Certain environmental factors, such as urban or rural residence, type of housing, food supplies, occupation, wages, etc., have long been known to show a correlation with the tuberculosis death rate in groups better or worse situated in these regards. That these are potent factors in increasing the incidence of infection with tuberculosis in a community and in activating latent infections is scarcely disputable. Indeed, under the strain of the extreme conditions of malnutrition, crowding, overwork and exposure engendered by the World War, the death rate from tuberculosis in the chief combatant nations rose abruptly during the war years. When, however, one considers the fifty years from 1883 to 1933 in this country, during which the fall in death rate from this disease from approximately 360 to 60 per 100,000 has occurred, it is apparent from the details available that no change in purely environmental factors is sufficient to explain what has occurred. The rate has fallen in urban as well as in rural communities during this period, it has fallen in spite of a tremendous influx of country dwellers into the cities, it has fallen even in the crowded slums, even in the more dangerous occupations, and it began its fall in a period of low wages and unemployment and has continued to fall through several panics and notably through the recent unexampled depression. It seems evident that some more fundamental cause exists for the regression of tuberculosis than variations in purely environmental factors.

¹ FLATZECK-HOFBAUER, ALFRED. *Kommen und Gehen der Tuberkulose*, Curt Kabitsch, Leipzig, 1931, p. 102.

² LONG, ESMOND R. The rise and fall of tuberculosis in certain American peoples, *Puerto Rico Jr. Publ. Health and Trop. Med.*, 1935, x, 270-287.

³ DROLET, GODIAS J. Epidemiology of tuberculosis, in *Goldberg's Clinical Tuberculosis*, Vol. I, p. A3-A61. F. A. Davis Co., Philadelphia, 1935.

⁴ WHITNEY, JESSAMINE S. New and supplementary facts and figures about tuberculosis, National Tuberculosis Association, New York, 1935.

It might be assumed that, following the discovery of the contagiousness of tuberculosis in 1865 and the isolation of the tubercle bacillus in 1882, the consequent gradual development of a great international campaign against this disease was the potent factor leading to its increasing control. The history of this movement, however, shows that it was merely in its infancy during the first twenty-five years of the falling tuberculosis death rate. Even today when there are estimated to be 73,000 beds for tuberculous patients in the United States and over 8,000 public health nurses devoting some of their efforts to the campaign against this disease, it is probably true that anti-tuberculosis measures are not the underlying cause of the continuing subsidence of the disease, though they undoubtedly constitute our most effective method of hastening its decrease in our communities. The difficulties of control measures are better realized when it is stated that there are probably between four and five hundred thousand cases of clinically active tuberculosis in the United States and that the relatively scant data available as to the incidence of infection in the total population would suggest that over 50 per cent have been attacked.

In recent times there is a growing tendency among students of this disease to pay more heed than formerly to the development of racial resistance as possibly the chief factor in its diminution as a cause of death. According to this conception the last fifty years in this country constitute a waning phase of a long drawn out epidemic of tuberculosis.

The word epidemic used in this connection may sound a little strangely and yet there exist a number of reported instances which illustrate clearly the possibility of relatively brief and acute epidemics of tuberculosis. Among the Canadian Indians placed in the Qu' Appelle reservation about 1880 the disease became epidemic about 1884. By 1890 the mortality rate had reached a height of 9,000 per 100,000. It then began to fall relatively rapidly and reached 1,000 per 100,000 in 1907. It remained at close to this level until 1926 and then fell rapidly to 273 per 100,000 in 1931. During the height of the epidemic an acute generalized form of the disease predominated, as the epidemic subsided the dominant type was a chronic one. The incidence of glandular involvement in the population was estimated at 33 per cent in the '90's, whereas in 1932 less than 1 per cent of the school children were found to have this malady. This outbreak as recorded by Ferguson⁵ is a classical example of the epidemic characteristics of tuberculosis in a susceptible race. There are excellent records also of the wave-like spread of tuberculosis in the Scandinavian countries from the cities in the south where it raged in the last century to the sparsely settled northern regions where the highest rates are now observed.

In support also of the influence of human resistance in altering the epidemic characteristics of tuberculosis may be cited the known differences in racial and national resistance to tuberculosis as observed in some of the

⁵ FERGUSON, R. G. The Indian tuberculosis problem and some preventive measures, Trans 29th Annual Meeting Nat Tuberc Assoc, 1933

larger cities of this country Throughout the country the tuberculosis mortality among Negroes is very much higher than among whites, in 1931 in the registration area the rate for whites was 49.7 and for colored was 171.9 That this higher rate cannot be due merely to greater opportunity for infection is indicated by the fact that tuberculin testing in childhood in New York does not show any higher incidence of infection among the colored than among the white children, the difference in mortality rates in these races in this city (white, 52, colored, 260) must depend, therefore, on the difference in ability to combat the infection after it has been acquired This is borne out by the suggestive studies of Asserson⁶ who found in testing babies of different national origins that all were infected at practically the same rate, but that when the positive reactors were later followed up 10 per cent of the Irish babies had died, 5 per cent of the Italian, 3.5 per cent of the American and 1.2 per cent of the Jewish

The importance of this factor of racial resistance is again indicated by the repeated observations which show that in races with low resistance and high mortality rates there is a preponderance of deaths in infancy and the preadult years, a high occurrence of rapidly generalizing forms, of massive exudative lesions and of lymph gland involvement, whereas in nationalities in which the tuberculosis mortality has fallen to a low level there is a great decrease in mortality from the disease in infancy, the peak of the death rate occurs in those over 40 years of age and the characteristic pathological changes of the disease are chronic localized fibrotic lesions in the lungs It seems that by a study of the age incidence of the deaths, the frequency of the various clinical forms and the distribution and character of the pathological lesions one might assess the progress made by any racial strain toward effective resistance to the disease

It is too early to do more than speculate about the character of this resistance to the extension of tuberculous infection There are two factors, however, which seem self evident At the stage of a tuberculosis epidemic where the greatest number of deaths occurs in infancy and childhood, the nation involved is being subjected to a drastic process of selection whereby only the more resistant survive long enough to propagate the race In the second place no degree of resistance has yet been developed which in the face of exposure to the disease will keep down to very low levels the incidence of infection

Analysis of the statistics of tuberculosis in the United States suggests that national resistance to the disease is growing steadily higher If the death rate continues to fall the number of active cases will eventually shrink to manageable proportions In this phase control measures may deal the decisive blow

It would not do to close upon this optimistic note without in fairness pointing to the reverse of the shield There is every reason to believe that a population in which there is very little tuberculosis becomes in time a

⁶ ASSERSON, M. A. Tuberculosis in infants, *Am Rev Tuberc*, 1927, xvi

population highly susceptible to rapidly fatal forms of the disease. It has already been noted that there is an increasingly high proportion of tuberculin negative young adults in the entering classes of our schools. These must be looked upon as a large group of persons who have escaped exposure to infection. The interesting observation has been made in certain training schools for nurses that it is in this tuberculin negative group that the majority of the active clinical cases of tuberculosis develop. This may indicate that we are already beginning to develop a group of people in this country who survive not by virtue of resistance to tuberculous infection, but by grace of fortuitous lack of exposure.

We may conclude that unless it prove feasible to completely exterminate tuberculosis we shall be saved from recurring epidemics due to loss of racial resistance only by the discovery of some immunizing agent.

REVIEWS

Behavior Development in Infants, a Survey of the Literature on Pre-Natal and Post-Natal Activity, 1920-1934 By EVELYN DEWEY, New York, published for the Josiah Macy, Jr., Foundation, by Columbia University Press

This book deals primarily with literature which has accrued since 1920 covering the fetal period and the first two years of life. The references are confined to the theories drawn from psychology and biology on the fundamental processes underlying growth and development of behavior, and to objective studies of fetal and infant behavior.

The material is organized as follows: Part I, growth processes—theories of behavior development, evidence from biology and neurology, correlation of structure and function from animal studies, Part II, behavior of the human fetus, Part III, neonatal behavior, Part IV, behavior during infancy, Part V, summary and conclusions. A bibliography of 216 titles is included.

The writer has avoided mere citations and direct quotations from the various authors and has instead attempted to assimilate and interpret the mass of ideas which has gathered around the development of certain types of infant behavior. The individual abstracts are extremely well written and the entire book is so organized as to provide continuity of thought, which makes for sustained interest and readability.

The literature surveyed covers a period during which there has been great progress in technique of research in infant behavior. The book is an invaluable reference handbook for those who are interested in the problems covered, including not only physicians, but psychologists and biologists as well.

A J R

Practical Neurological Diagnosis, with Special Reference to the Problems of Neurosurgery By R. GLEN SPURLING xi+233 pages, with 99 illustrations. Charles C. Thomas, Springfield, Illinois. 1935. Price, \$4.00.

Anyone who has had the task of presenting clinical neurology to undergraduate students will appreciate the motive which led the author to compile "a simple account of the principles of neurological diagnosis." The method of presentation of the subject in teaching, as well as in such a treatise, is always a matter of concern. What shall be stressed and what shall be omitted? Is it better to "cover the field" and leave the average student with a hodge-podge memory of neurology, or present the kernel of elementary neurology so that he at least can recognize the common disorders of the nervous system?

The author has chosen to present the basic facts which he feels will give the student a working knowledge. The book is divided into three parts: neurological examination, cerebrospinal fluid, and x-ray diagnosis. The first part consists of seven chapters in which the chief subdivisions of the nervous system are covered. The opening chapter deals with the patient's history and gives several important points in history-taking. A little more detail here would have been advantageous. A well-taken neurological history will often tell the practitioner that something is wrong with the nervous system when an examination alone might fail. The cranial nerves are taken up in order. There is a brief anatomical review for each with the clinical application and the technique of examination. This section is very well done. The cerebrum and cerebellum are similarly presented in Chapters 3 and 4. A text written by a neurosurgeon would naturally devote considerable space to these subdivisions because of the great importance of cerebral localization in neurosurgery. However,

it seems that 14 pages devoted to the frontal lobe is a little out of proportion to the brevity used elsewhere, especially when one realizes that the physiology of this lobe still presents many unanswered questions. Only proved clinical facts would seem to have a place in an outline of this type. The examination of the motor and sensory systems is discussed in the chapter on the spinal cord. The presentation here seems a bit disjointed and lacking in perspective. The chapter dealing with reflexes is very well done.

The section on the cerebrospinal fluid is clear and concise. The technic of lumbar puncture, the examination of the fluid, and cerebrospinal fluid dynamics are discussed.

The final chapter deals with roentgen-ray diagnosis, including routine skull examinations, air injections, and lipiodol technic.

The book is up to the usual quality of this publisher. It is well illustrated with 99 well-chosen diagrams and photographs. The bibliography contains 18 titles. Students will find this book of interest.

J G A, JR

Around a World on Fire By KARL E. KASSOWITZ. 198 pages, 14 × 19.5 cm. Gutenberg Publishing Company. 1935. Price, \$2.00.

The World-War gave rise to many strange and thrilling journeys, only a few of which have been printed. The story of Dr. Kassowitz's experiences as an Austrian army surgeon attached to combatant troops, his capture by the Russians and removal to Siberia, his escape with a comrade and flight in Chinese disguise across the frozen wilderness of North China to the relative safety of the Austrian Legation in Peking and his eventual return to Austria after imprisonment by the British at Gibraltar,—all this high adventure is told vividly and modestly and almost too briefly in this attractive little volume.

M C P

Diagnosis and Treatment of Disorders of Metabolism By JAMES S. McLESTER, M.D. 328 pages, 24 × 15.5 cm. Oxford University Press, New York. 1935.

This book reflects the conventional viewpoint concerning metabolic disorders as understood and written about a decade or two ago. The subjects treated include gout, obesity, diabetes, and disorders of the intermediary metabolism, which embrace uraturia, oxaluria, phosphaturia, cystinuria, alkaptonuria, hemochromatosis and pentosuria. Aside from diabetes there is no mention of other endocrine diseases or any hint that these also are important disorders of metabolism. There is nothing about disturbances of calcium metabolism, or of thyroid dysfunction, although basal metabolism is mentioned. If obesity is discussed, it would seem necessary to treat of undernutrition also. The chapter on disturbances of the water balance is highly inadequate. That on acidosis contains directions for various chemical determinations for which the reader might better be referred to one of the standard laboratory manuals. Some of the directions for determination of the plasma carbon dioxide capacity, for the determination of its hydrogen-ion concentration and for estimation of the alveolar carbon dioxide tension, are obsolescent, and indicate lack of recent familiarity with the procedures.

Altogether this is not a very adequate book and cannot be conscientiously recommended.

G A H

The Diseases of the Endocrine Glands By HERMANN ZONDEK, M D (Berlin) 492 pages, 25 × 18 cm William Wood and Company, Baltimore 1935 Price, \$11 00

The author is one of the several eminent internists lost temporarily, at least, to Germany by reason of the political upheavals of the past few years. He is a member of a family prominent in medical science. His brother's name linked with that of Aschheim is widely known in connection with a test for pregnancy. The author's reception in England where he worked for some time in Manchester before going to Palestine doubtless led to this revision of the 1926 German edition of his work and to the excellent translation by Prausnitz.

"Primarily a book for the clinician," it is admirably adapted to this purpose. The first or general part occupies 105 pages of this nearly 500 page volume and contains eleven chapters including those on the relations between the different glands, the physiology and chemistry of the hormonal glands, hormones and vitamins, the vegetative nervous system and its relations to the hormonal system, methods for the examination of patients and general remarks on organotherapy.

It is in the second or special part comprising four-fifths of the volume that the unusual arrangement will appeal particularly to the clinician. Here are considered definite clinical pictures, e.g., Graves' disease, myxedema, tetany, obesity, diencephalopathy, acromegaly, dwarfism, osteomalacia, osteitis fibrosa. Addison's disease, diseases of the generative system and others. The subjects are presented as problems in internal medicine and the glandular and hormonal factors are fully discussed. Case reports and illustrations are taken from the author's own patients.

His points of view as a rule are logical and conservative. To quote a paragraph from the preface, "A number of fundamental hypotheses some of which were derived from the author's personal work on the hormone problem, run through the book and give it its special outlook. As instances the following may be cited: (1) Hormone effect is not an absolute but a variable quantity, depending not least upon the momentary condition of the organ on which it acts, more especially the physico-chemical conditions of its cells, (2) Functional and anatomical changes in endocrine glands should not always be regarded as the cause of disease, but in many cases as the reactions of the glands to morbid processes primarily located in certain other organs, (3) With phylogenetic evolution and progressive differentiation of cellular functions, the hormone appears on the scene as the intensifier of such functions, even in the most highly developed beings, however, not all of them are indispensable to life, (4) The endocrine system is but one link in the chain of vegetative functions of the organism. This should be emphasized in order to avoid the danger of overestimating the role of the hormonal factors."

The book may be highly recommended to the clinician for whom it was prepared

T P S

Practical Endocrinology Symptoms and Treatment By MAX A. GOLDZIEHER, M D 358 pages, 22 × 15.5 cm D Appleton-Century Company, New York City 1935 Price, \$5 00

The author is entitled Endocrinologist, Gouverneur Hospital, Chief of Endocrine Clinic, Gouverneur and Brooklyn Woman's Hospitals, former Professor of Pathology, Royal Hungarian University, Budapest. He has been an active worker in this field for many years and is the author of another book, "The Adrenals."

"Practical Endocrinology" is quite a readable book, it is divided into short chapters and is expressed in a simple and direct style. The arrangement of subject matter is pleasing to the reviewer but may quite possibly offend other readers. There are three short introductory chapters on morphology and physiology of the endocrine

glands and on the examination of the patient. Following sections relate to Disturbances of Development and Growth, Disturbances of Nutrition, Disturbances of Metabolism, etc., with, in closing, a brief and succinct section on treatment. The reader must use the index and turn many leaves to get the full picture of a definite disease, e.g. Graves' disease or myxedema.

The author seems a sufficiently ardent therapist, somewhat conservative toward surgery and x-ray treatments but leaning rather heavily on organotherapy. He recommends pituitary and adrenal tablets by mouth in addition to similar products parenterally. He also describes methods of physical therapy, diathermy and light treatment, adapted to the endocrine organs.

The book was written and arranged for the general practitioner. It expresses the ideas and opinions of the author without argument or discussion. There are no references to the work of others. It is not therefore a good work for students if their skepticism is to be stimulated by differences of opinion, but the book will doubtless be highly valued by those who know the author well and who have great confidence in his opinion.

T P S

COLLEGE NEWS NOTES

NEW LIFE MEMBERS

The total number of Life Members in the American College of Physicians has been increased to fifty-eight. The following Fellows have become Life Members since January 1, 1936, their listings being in the order of their accession:

Dr Casper H. Benson, Columbus, Ohio
Dr Donald Gregg, Wellesley, Mass
Dr James Ray Arneill, Denver, Colo
Dr Thomas Fitz-Hugh, Jr., Philadelphia, Pa
Dr C. Charles Burlingame, Hartford, Conn
Dr Noble Wiley Jones, Portland, Ore
Dr Cecil M. Jack, Decatur, Ill
Dr Roy M. Van Wart (formerly of New Orleans, La.), Descanso, Calif

The members of the Board of Regents of the College have joined in issuing a personal invitation to the Governors to a dinner to be held in Detroit on Sunday evening, March 1, prior to the opening of the Clinical Session.

STATE MEETING OF COLLEGE MEMBERS IN LOUISIANA

Under the Chairmanship of Dr Joseph E. Knighton, Governor of the College for Louisiana, a combined scientific and social meeting was held at Shreveport on January 30, 1936. The meeting was conducted particularly for those Fellows and Associates of the College residing in and about Shreveport, and was attended by some guests, one of whom was the President of the local organization representing the American College of Surgeons.

Dr T. P. Lloyd discussed subacute bacterial endocarditis, with a report of a case; Dr W. S. Kerlin discussed pernicious anemia and exhibited a patient showing the characteristic achylia and neurological changes, but only minor blood changes; Dr A. A. Herold discussed recent developments in the treatment of diabetes.

The scientific discussions were followed by a dinner and a delightful evening of good fellowship. Similar meetings are planned for the future.

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the following gifts to the College Library of publications by members. Special emphasis is placed on gifts of books of which members are the authors, for the College is desirous of obtaining particularly all books written by its members.

Dr Sigmund S. Greenbaum (Fellow), Philadelphia, Pa.—one autographed book, "Diseases of the Mouth and Their Treatment."

Dr J. Arthur Myers (Fellow), Minneapolis, Minn.—two books, "Modern Aspects of Diagnosis, Classification and Treatment of Tuberculosis" and "The Child and the Tuberculosis Problem."

Dr Linn J. Boyd (Fellow), New York, N. Y.—one translation, August Bier's "Study on Inflammation."

Dr Walter L Bierring (Fellow), Des Moines, Iowa—one reprint, "The Social Security Act"

Dr Herbert T Kelly (Fellow), Philadelphia Pa—one reprint

Dr Alfred J Scott, Jr (Fellow), Los Angeles, Calif—one reprint

Dr John W Torbett (Fellow), Marlin, Texas—two reprints

Dr Stephen H Curtis (Associate), Troy, N Y—six reprints

Dr William B Grayson (Associate), Little Rock, Ark—two reprints

Dr R R Hendershott (Associate), Tiffin, Ohio—one reprint

At the Fourth Annual Symposium on Heart Disease of the Los Angeles County Heart Association, during December, the following Fellows contributed as indicated

Dr John C Ruddock—"Coronary Occlusion"

Dr B O Raulston—"Circulatory Edema"

Dr E Richmond Ware—"Pulmonary Embolism"

Dr R Manning Clarke—"Paroxysmal Tachycardia"

Dr A M Hoffman—"Peripheral Vascular Failure"

Dr Donald J Frick—"The Use of Drugs in Cardiovascular Disease"

Dr A S Granger—"Diet in Heart Disease"

Dr Howard F West—"The Challenge of Arteriosclerosis"

The Guilford County Medical Society recently awarded to Dr Frederick R Taylor, High Point, N C (Fellow), a plaque for the most "outstanding contribution" to medical literature contributed by members of the society during the past year. Prominent among Dr Taylor's contributions was a chapter in Oxford Medicine on "Arachnidism—The Clinical Effects of Spider Bite"

Dr Mary O'Malley (Fellow), for many years Clinical Director of St Elizabeths Hospital, Washington, D C, has resigned that position and retired from active practice. She is now residing in Buffalo, N Y

Dr Salvatore Lojacono (Fellow) has resigned the Superintendency of Morgan Heights Sanatorium at Marquette, Mich, effective January 25, 1936, and is now located in Lansing

Dr Walter P Gardner (Fellow) has resigned from the Hastings State Asylum at Hastings, Minn, to accept the Medical Directorship of the Fergus Falls State Hospital at Fergus Falls, Minn. This is a two thousand bed hospital for psychiatric cases

Dr Edward Weiss (Fellow), a member of the Department of Medicine of the Temple University Medical School, has been made Professor of Clinical Medicine in that Institution

Dr Constantine P Faller (Associate), Harrisburg, Pa, has been awarded the biennial Seibert Prize of \$500.00 for study in Europe of the Harrisburg Academy of Medicine

Dr Joseph I Linde (Fellow), Clinical Professor of Pediatrics, Yale University School of Medicine, is the Health Officer of New Haven

Dr Edwin C Swift (Fellow), Jacksonville, Fla , is the President of the Florida East Coast Medical Association for the present year

Dr Arthur U Desjardins (Fellow), Rochester, Minn , and Dr Walter M Simpson (Fellow), Dayton, Ohio, are members of the American Committee for the International Conference on Fever Therapy to be held in New York City during September, 1936 Therapeutic, physiologic and pathologic phases of fever will be discussed All papers presented will be translated in abstract form into French, English and German

Dr Thomas F Sellers (Associate), Atlanta, Ga , is Secretary of the newly organized Georgia Association of Pathologists

Dr William Henry Walsh (Fellow), Chicago, has been appointed as a consultant to study the hospital needs of the Institute of Tropical Medicine at San Juan, Puerto Rico

Dr Robert A Black (Fellow), Chicago, has been appointed a member of the Chicago Board of Health

Dr Reginald Fitz (Fellow), Boston, Mass , for many years Associate Professor of Medicine at Harvard University Medical School, has been appointed Professor of Medicine in the Boston University School of Medicine and Director of the Robert Dawson Evans Memorial, the department of research and preventive medicine of the Massachusetts Memorial Hospitals

Dr Hyman I Goldstein (Associate), Camden, N J , delivered addresses during the past year before the Congress on Gout and Uric Acid at Vittel, France, the International Congress of the History of Medicine at Madrid, Spain, and before the Pazmany Peter Royal University of Budapest

Dr Lewis J Moorman (Fellow), Oklahoma City, was recently named to Oklahoma's Hall of Fame by the Oklahoma Memorial Association in recognition of his achievements in medicine Dr Moorman is a former Dean of the University of Oklahoma School of Medicine and ex-President of the Oklahoma State Medical Association and an ex-President of the Southern Medical Association

Dr Alvan L Barach (Fellow), Columbia University College of Physicians and Surgeons New York City, has received a grant from the National Research Council for research in the therapeutic use of helium

Dr Raymond G Taylor (Fellow), Los Angeles, was elected one of the Vice Presidents of the Radiological Society of North America at its last annual meeting

Dr Frank H Redwood (Fellow), Norfolk, Va , was elected a Vice President of the Seaboard Medical Association at its last annual meeting

Dr John G FitzGerald (Fellow), Dean of the Faculty of Medicine and Director of the School of Hygiene and Connaught Laboratories, University of Toronto, delivered the annual Morris Hertzstein lectures, March 2-4, under the auspices of the Medical Schools of Stanford University and the University of California

Dr Millard E Winchester (Fellow), Brunswick, Ga , has been reelected Secretary of the Georgia Public Health Association for 1936

Dr Herbert A Burns (Fellow), Superintendent of the Minnesota State Sanatorium for Consumptives at Ah-Gwah-Ching, has also been placed in charge of a new annex erected exclusively for treatment of Indians. The Indian annex will be under the direction of the State Board of Control, in cooperation with the Federal Office of Indian Affairs. It is said to be the first sanatorium in the United States for Indians, excepting a small inadequate one at Onigun on Leech Lake, which has now been destroyed by fire and the patients transferred to the new institution

Dr Anthony Bassler (Fellow), New York City, was elected President of the National Society for the Advancement of Gastro-Enterology at its annual meeting in New York during December

Dr Elliott P Joslin (Fellow), Boston, Mass , delivered the Eastman Memorial Lecture, January 10, on "Diabetes of Today and Tomorrow," in connection with the tenth anniversary of the opening of the University of Rochester School of Medicine and Dentistry, Strong Memorial Hospital and the School of Nursing



CHARLES GODWIN JENNINGS, M.D., F.A.C.P.

OBITUARIES

CHARLES GODWIN JENNINGS

Charles Godwin Jennings was born at Leroy, New York, February 4, 1857, of the union of Thomas A. Jennings and Matilda Godwin. He began his education in the public schools of Seneca Falls, New York, and graduated in 1875 from Mynderse Academy. In the same year he began the study of medicine in a preceptor's office, where he remained until October 1876, when he entered Detroit Medical College from which he graduated, with the degree of Doctor of Medicine, in 1879.

During his Senior year he served as undergraduate interne in St. Luke's Hospital and upon graduation received the appointment of Resident Physician. In May 1880 Dr. Jennings began the practice of medicine in Detroit as Assistant to Dr. E. L. Shurley. Thus it is that Dr. Jennings practiced his profession in the city of his adoption continuously for fifty-six years. No truer estimate of the quality and scope of that long period of beneficent service to the public and his profession can be noted than the erection in 1930 of the Charles Godwin Jennings Hospital on Jefferson Avenue, largely by devoted friends and patients as an enduring testimonial of the appreciation, admiration and affection in which he was held by those who knew him best.

At one time or another he had held commanding positions on the staffs of all the Hospitals of his city. At the time of his death, Dr. Jennings was Chairman of the Board of Trustees and of the Medical Board and attending physician of the Charles Godwin Jennings Hospital. He was consulting physician to the Harper Hospital, the Grosse Pointe Hospital, the Children's Free Hospital, the Detroit Tuberculosis Sanitarium, and to the U. S. Marine Hospital.

In the period between 1881 and 1920 Dr. Jennings was a member of the Faculties of the Detroit Medical College and the Detroit College of Medicine and Surgery. Beginning his teaching as Lecturer in Chemistry he successively occupied the chairs of Professor of Chemistry, Professor of Diseases of Children, Professor of Practice of Medicine and Diseases of Children and finally Professor of Medicine. Dr. Jennings was a member of many medical societies and associations, among which are the American Medical Association, American Climatological Association, American Therapeutic Society, American Pediatric Society, The Michigan State and Wayne County Medical Societies and the American College of Physicians, in which he took an active part during the twenty years of his membership, having been Vice-President, Regent and Chairman of the Board of Governors. At the time of his death Dr. Jennings was Chairman of the Committee on Arrangements for the Annual Meeting in Detroit this year.

Dr Jennings was 1st Lieut , Medical Reserve Corps, U S Army, 1911 to 1917, Captain, Medical Corps, U S Army, 1917-1919, on duty Camp Grant , member Central Examining Board at Detroit 1911-1918

He had been a member and President of the Detroit Board of Health, member of Gorgas Memorial Institute, etc

The University of Michigan conferred upon him the honorary degree of Master of Arts and from the College of the City of Detroit he received the honorary degree of Doctor of Science

Dr Jennings was a prolific reader. He was Associate Editor of the *Annals of Clinical Medicine* and of the *Archives of Pediatrics*, Editor of *The Microscope*, 1885-1890, contributor to Tice's Practice of Medicine, Therapeutics of Internal Diseases, and to the Cyclopedia of Diseases of Children

Dr Jennings was a member of the Yondotega, the Wilenagemota and the Grosse Pointe Clubs, as well as the Sons of the American Revolution

It is not for his professional, scientific, literary or civic attainments, however outstanding, that Dr Charles Godwin Jennings will be remembered by his colleagues far and near, but for the qualities of heart and mind, and the gift of true friendship possessed to the highest degree by this kindly gentleman. His charming personality, his keen sense of humor and his generous devotion to his friends, his colleagues and his students, won for him the confidence and affection of men and women throughout the United States and Canada. As evidence of the esteem in which he was held in his own State a testimonial dinner was given him on February 28, 1934, by the Wayne County Medical Society, on the fifty-fifth anniversary of his graduation in medicine. This dinner was attended not only by men prominent in medicine, dentistry and the civic leaders of the State, but also by colleagues from all parts of the country.

One of the underlying causes for Dr Jennings' continued physical fitness, his alertness of mind and his unquenchable enthusiasm for his profession and for life in general was his devotion to his hobbies, namely fly-fishing and hunting, in each of which he was an expert. Each year saw him off to the great open spaces for several weeks with rod and gun.

Fortunate indeed were those of his close friends who were able to accompany this ardent sportsman and nature lover.

Few men, who have gone on the long journey, from any walk in life, are missed so acutely by as large a circle of loyal and devoted friends as is this great physician.

WILLIAM GERRY MORGAN, F A C P

DR HENRY WALD BETTMANN

Dr Henry Wald Bettmann (Fellow), Cincinnati died December 5, 1935, aged, 67 years

Dr Bettmann was born in Cincinnati, attended public schools in that city, and graduated with highest honors at the University of Cincinnati. He was a charter member of the Cincinnati Chapter of Phi Beta Kappa. During his undergraduate days at the University he was a prominent member of the football team. In 1889 he graduated with high honors from the Medical College of Ohio (University of Cincinnati). After serving his internship at the Cincinnati Hospital, he spent two years in postgraduate work abroad, chiefly in Berlin, Vienna and Prague. On his return to Cincinnati in 1893, he began general practice but continued his scientific work at the Cincinnati Hospital. While serving as curator of the laboratory he originated the first city-wide service for the bacteriological diagnosis of diphtheria, and with a group of colleagues gave the first course on clinical microscopy in Cincinnati.

In 1894 Dr Bettmann was appointed pathologist to the Cincinnati Hospital. During the years that followed, he did much investigative work and published many papers and in 1905 he won the Alvarenga prize for his monograph on "The Shape and Position of the Stomach." He served as pathologist until 1907, when a serious autopsy infection forced his resignation.

Early in his practice, Dr Bettmann became interested in gastro-enterology. He was a charter member of the American Gastro-Enterological Society and was its President in 1920.

In 1921 he was appointed Director of the Medical Service of the Jewish Hospital of Cincinnati, and inaugurated the weekly clinical conferences at that institution, which he directed until his death.

In 1931 he was made Professor of Medicine in the University of Cincinnati College of Medicine, having held the rank of Associate Professor for a number of years previously. His course in gastroenterology was an outstanding one.

The claims of a large practice did not prevent his filling many other positions. He was President of the Academy of Medicine, Cincinnati, in 1927. He was one of the founders, and for many years a member of the governing body of the University School of Cincinnati. For over twenty-five years he was an active member of the board of the Public Library. He was intensely interested in belles lettres and had a profound knowledge of the masterpieces of English, French and German literature.

He was an amateur botanist of distinction, he was a world authority on chess problems. To his patients he was indeed the beloved physician. To his friends, his charm, his goodness and his loyalty were real sources of inspiration. He was an honor to his profession and his life work will endure. Of him it might well be said, "He loved truth and beauty and he never did an ignoble thing."

ALFRED FRIEDLANDER, M D , F A C P

ERRATUM

"Chemical Studies in Myasthenia Gravis," by M. Adams, M. H. Power and W. M. Boothby. The sentence which begins in the last line of page 825 of the January issue should have read: If the five patients (cases 11, 3, 12, 13 and 14), who were all 65 years of age or more, and obese, are excluded from consideration, the coefficients of the remaining patients will be found to vary from 6.6 to 9.7.

ANNALS OF INTERNAL MEDICINE

VOLUME 9

MARCH, 1936

NUMBER 9

LONG-STANDING CASES OF AURICULAR FIBRILLATION WITH ORGANIC HEART DISEASE, SOME CLINICAL CONSIDERATIONS^{*}

By WILLIAM A. EVANS, M.D., F.A.C.P., *Boston, Massachusetts*

THE onset of auricular fibrillation is generally considered an unfavorable event in the course of organic heart disease. The reports in the literature indicate that the average duration of life after the onset of fibrillation is a matter of a few years comparable to that following the onset of malignant neoplastic disease. White¹ gives two to three years as the average duration. Of a group of 173 fatal cases Willius² found the average duration one year and three months. In 20 cases of auricular fibrillation associated with rheumatic heart disease Jones³ found an average duration of three years and six months. Clerc and Stieffel⁴ observed 54 per cent of their cases living a year or more and only 9 per cent over three years. Frick and Kennicott⁵ reported an average duration of five years and eight months in a group of cases observed to exitus, while Cookson's⁶ averages are five and one-fourth years for the rheumatic group and seven years in the non-rheumatic group. Thus in the more recent studies with perhaps longer periods of observation the outlook in auricular fibrillation appears to be more favorable. A few isolated instances of auricular fibrillation of unusually long duration have been reported. The longest is that of Heitz,⁷ a case of non-valvular heart disease with fibrillation observed over a period of 32 years. He also reports two cases of 10 and 12 years' duration. Vaquez⁸ observed a case for 12 years. Laslett's⁹ report is of a case of 15 years' duration, and he mentions a case of Cowan's surviving almost 12 years. In the group studied by Frick and Kennicott, instances of fibrillation observed for 20, 16, 15, 13 and 12 years are recorded.

The purpose of the present study was to analyze a group of cases of organic heart disease known to have persistent auricular fibrillation for a long period of time and to determine what features may have contributed to their longevity. Cases of transient auricular fibrillation were excluded. From the records of the Peter Bent Brigham Hospital and of the private

^{*} Received for publication September 5, 1935.

From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts.

practice of S A Levine of Boston, 39 such cases were collected. The duration was regarded as being from the time at which auricular fibrillation was first recognized clinically until the time the patient was last seen. Inasmuch as in many instances the onset of auricular fibrillation must have antedated by years or months the time of clinical recognition and inasmuch as 26 or two-thirds of the cases are known to be still alive, the actual duration must be really much longer. Ten in the group are known to be dead and three are lost. At the time of onset the diagnosis was usually confirmed by the electrocardiogram, but in a few instances the diagnosis was considered to be established with certainty when made by a number of observers at different times clinically. In this group the duration of observed fibrillation was at least 8 years, the upper limit being three cases of 15, 17, and 18 years respectively, and the average duration for the whole group 10.3 years. The average duration in the rheumatic group was 10.0 years, as compared with 10.6 in the non-rheumatic group.

SEX

The sex incidence in the whole group was not remarkable, there being 22 males and 17 females, or 56 per cent and 44 per cent, respectively. In the rheumatic group there was a predominance of females (41 per cent versus 59 per cent), while in the non-rheumatic group there was a predominance of males (76 per cent versus 24 per cent). The slight predominance of males is quite similar to that found by Lewis,¹⁰ Willius,² Brachman¹¹ and Mohler and Lintgen¹² in unselected groups of cases with auricular fibrillation. Campbell¹³ and Levine¹⁴ observed an equal distribution, and White¹⁵ a slight predominance of females, while Cookson⁶ in a large group found twice as many females as males.

AGE

There have been many reports of the age incidence in auricular fibrillation and eight of these have been charted (figure 1). There is the same

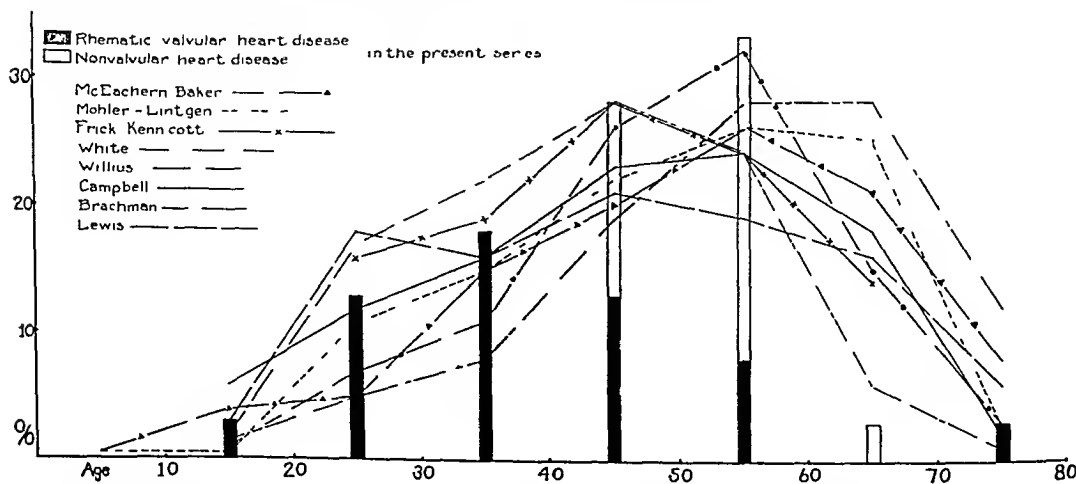


Fig 1 Age incidence in auricular fibrillation of unselected groups of cases obtained from the literature compared with the age incidence in this series of long-standing fibrillation.

general shape and character to these curves, and they offer a satisfactory standard for comparison with our group. Here the age taken was that at the time at which auricular fibrillation was first recognized. It is apparent that the cases of long duration may occur at about any age but that they are most common in the fifth and sixth decades as with unselected cases of auricular fibrillation. The close agreement of the curves indicates that the age of the patient at the time of onset has little to do with the prognosis. When the valvular and non-valvular cases are analyzed separately, slight differences are detected which may have significance, and this will be discussed below.

INCIDENCE OF ASSOCIATED HEART DISEASE

A number of reports on the incidence of associated heart disease are available, and these have been tabulated for comparison (Table 1). Here

TABLE I
Type of Heart Disease Associated with Auricular Fibrillation

Authors	Number of Cases	Rheumatic Heart Disease per cent	Non-Rheumatic Heart Disease per cent				
			Artero-sclerotic	Hyper-tensive	Thyroid	Syphilitic	Unclassified
Mohler, Lintgen ¹⁹	220	42	32		4.6	1.4	20
Levin ²²	33	64	15		9	3	9
Clerc, Stieffel ⁴	75	65					
Coffen ¹⁸	37	62					38
Campbell ¹³	100	53	36		11		
Brachman ¹¹	359	62	32		3	2	
Levine ¹⁴	128	36	31				34
Cookson ⁶	361	69	22		7	2	
Stroud, Laplace, Reisinger ²⁰	253	48	35		4	9	4
McEachern, Baker ¹⁶	575	34	31	17	8	3	7
Frick, Kennicott ⁵	51	49					51
Yater ²¹	145	20		8	44	1	27
Lewis ¹⁰	141	54					46
Willius ²	500	31		20	33		16

the agreement is not so satisfactory, partly because of different terminology and criteria for diagnosis, partly because of the variable incidence of such diseases as rheumatic fever and toxic goiter in different localities and possibly also because of a greater interest in certain types of disease in different institutions. However, certain general features are available for comparison.

Rheumatic heart disease occurred in 22, or 54 per cent, of our group, a figure one might reasonably expect to find in an unselected group. A diagnosis of mitral stenosis was made in all of the 22 cases. An additional

diagnosis of aortic insufficiency was made in six, two of which also had aortic stenosis. There is nothing peculiar about this distribution which would help in basing the prognosis on the kind of valve lesion. The average age of the patients at the time of onset of auricular fibrillation in this rheumatic group was 39.7 years. This compares with an average of 37 years found by Levine¹⁴ in a comparable group. This supports the view that in rheumatic heart disease auricular fibrillation is less serious if it occurs in older rather than in younger individuals.

Syphilitic heart disease is very rarely associated with auricular fibrillation, and it is not surprising that no instance of that type of heart disease appeared in our series. In the 31 cases in which the Wassermann test was carried out it was reported negative.

Hyperthyroidism was present at the time auricular fibrillation was recognized in two of the cases. However, the fact that fibrillation persisted after thyroidectomy and a restoration of the basal metabolism to normal limits would indicate that the hyperthyroid state was not alone responsible for the irregularity. Indeed one of the cases had rheumatic heart disease with mitral stenosis, and the other was approaching the older age group with a large heart, the enlargement being confirmed roentgenologically, when auricular fibrillation and hyperthyroidism were first recognized. In such a series one would not expect to find fibrillation of long duration associated with hyperthyroidism without underlying organic heart disease as well.

Non-Valvular Heart Disease Our series contains 17, or 44 per cent, of such cases, five of which (13 per cent of the total) might be considered to have hypertensive heart disease. The relative incidence of hypertensive heart disease was higher in the comparable studies of McEachern and Baker¹⁶ and Willis² so that hypertension would appear to be a somewhat unfavorable factor in this group. The average age at the onset of fibrillation in this group was 50.4 years, which is significantly less than the average of 58 years found by Levine¹⁴ in a comparable group of undetermined duration. Thus, here in contrast with the rheumatic group, the duration of life following the onset of fibrillation is longer in the relatively younger patients. Therefore, it seems that in the group studied there is a difference of about 10 years between the age of onset of fibrillation in valvular and non-valvular cases (39 years and 50 years), as compared with a difference of about 20 years in the two groups of unselected fibrillators.

STATUS OF THE HEART AND CIRCULATION AT THE ONSET OF AURICULAR FIBRILLATION

Heart Size It is generally accepted that a large heart indicates a poor prognosis. However, in this series the examination at the onset of fibrillation indicated some degree of enlargement in 32 instances, and in the others it may have been present but not recognized. In 19 instances the enlargement was marked and in five of these this was confirmed roentgenologically.

Hypertension At the outset of this study it was thought that evidence might be found showing that the presence of hypertension exerted a favorable influence on the course of mitral stenosis (Levine and Fulton¹⁷) However, the data seemed to be too meager either to prove or disprove this conception Of the 22 rheumatic valvular cases, only two were observed to have a systolic arterial tension above 150 mm of mercury during the entire period of observation Furthermore, the average blood pressure for the various decades as observed at the onset of fibrillation follows more closely the normal curve than that found by Levine and Fulton for mitral stenosis However, a number of our patients developed increasing pressures during the period of observation, five of them reaching pressures above 150 Thus, with seven of the 22 patients having or acquiring pressures above 150, it appeared that hypertension was a little more prevalent in the valvular group (average age 38.7 years) than one might have expected in the average population of the same age period

Of the 17 patients with non-valvular heart disease five had hypertension when first seen at the onset of fibrillation and in two hypertension developed

Objective Signs of Congestive Failure Persistent râles at the lung bases, enlargement of the liver or peripheral edema was noted in 16 cases at the onset of fibrillation In 19, no objective evidences of congestive failure were demonstrable although in some of these there was dyspnea and limitation of normal activity and later the development of congestive failure This compares with Campbell's¹³ observation that signs of failure are present in about one-half the cases of auricular fibrillation when seen for the first time Three cases were very striking in having greatly enlarged hearts and marked signs of congestive failure when first seen two of whom are still living after being followed for nine years and the other having been lost eight years after the onset of fibrillation

Ectopic Beats A few cases in this series were observed in the period just preceding the onset of fibrillation and they commonly had numerous premature beats Occasionally these beats were so numerous that differentiation from auricular fibrillation could only be made electrocardiographically According to White,¹ Wilhus,² Coffen,¹⁸ and also Clerc and Stieffel,⁴ extrasystoles associated with fibrillation indicate a poor prognosis In this series, however five cases were encountered in which the initial electrocardiogram showed premature ventricular beats as well as fibrillation Thus their presence cannot be taken to indicate necessarily an unfavorable outlook Apart from evidences of right or left ventricular preponderance no other electrocardiographic anomalies were encountered in the initial tracings

DISCUSSION

It is apparent that no clues to prognosis are offered by the evidence here analyzed From data obtainable upon examination of a patient at the inception of auricular fibrillation it would seem impossible to predict his life

expectancy in any but the most general way. The most important factor in his longevity is perhaps his good fortune in escaping the serious accidents of the type of heart disease from which he is suffering. In the rheumatic patient with auricular fibrillation the most common cause of death after congestive failure is embolism and pulmonary infarction (Laws and Levine¹⁹). Another frequent cause of death in the patient with rheumatic heart disease is subacute bacterial endocarditis, but it is well known that this is very rare in auricular fibrillation, and there was no instance of it in our series. At least one episode of embolism was noted in 10 of our patients during the period of observation, and many survived a number of embolic phenomena in various organs. In the older age group death is commonly brought on by the vascular accidents of hypertension and coronary artery disease. Coronary thrombosis is recognized as rare in the presence of fibrillation and was observed in only one of our patients during the period of observation. However, two others were known to have survived attacks at or prior to the onset of fibrillation. One patient survived a cerebral vascular accident associated with hypertension. In contrast to the rheumatic group there was a conspicuous rarity of embolic phenomena.

CONCLUSIONS

1. A study was made of a group of 39 patients with organic heart disease who were known to have had auricular fibrillation for long periods of time ranging from 8 to 18 years.

2. Of these 39 cases there were 22 with rheumatic valvular and 17 with non-valvular heart disease. There were no cases of syphilitic or thyroid heart disease.

3. There was a predominance of females in the valvular group and of males in the non-valvular group.

4. Cases were encountered in all decades from the second to the eighth inclusive. The age distribution was quite similar to that of unselected groups reported in the literature except for a slight tendency to an increased predominance of cases in the fifth and sixth decades at the expense of the seventh and eighth decades. The average age in the rheumatic valvular group was slightly older and in the non-valvular group slightly younger than in comparable unselected groups.

5. Hypertension appeared to be slightly more common in the rheumatic valvular group and slightly less common in the non-valvular group than one would expect in the comparable groups of undetermined duration.

6. The majority of the patients had enlarged hearts, some to an extreme degree, at the onset of fibrillation, and almost half had objective manifestations of congestive failure when first seen.

7. It is believed that these patients owe their longevity in large part to their good fortune in escaping or surviving the accidents to which patients

with cardiac disease in general are subject, namely embolism, subacute bacterial endocarditis, cerebral hemorrhage and coronary thrombosis

It is a pleasure to acknowledge the suggestions and criticisms of Dr S A Levine

BIBLIOGRAPHY

- 1 WHITE, P D Prognosis in heart disease in relation to auricular fibrillation and alternation of the pulse, *Am Jr Med Sci*, 1919, clvii, 5
- 2 WILLIUS, F A Auricular fibrillation and life expectancy, *Minn Med*, 1920, iii, 365
- 3 JONES, H W Some points in the prognosis of auricular fibrillation, *Lancet*, 1926, ii, 640
- 4 CLERC, A, and STIEFFEL, R Pronostic de l'arythmie complete, *Bull et mem Soc med d hôp d Paris*, 1927, li, 1139
- 5 FRICK, D J, and KENNICOTT, R H Auricular fibrillation, a review of a series of cases, *Calif and West Med*, 1928, xxviii, 779
- 6 COOKSON, H The etiology and prognosis of auricular fibrillation, *Quart Jr Med*, 1929-30, xxiii, 309
- 7 HEITZ, J Un cas d'arythmie complete permanente évoluant depuis trente-deux ans, *Arch d mal d coeur*, 1914, vii, 116
- 8 VAQUEZ Quoted by Heitz
- 9 LASIETT, E E A case of auricular fibrillation of 15 years' duration, *Lancet*, 1927, i, 1290
- 10 LEWIS T Clinical disorders of the heart beat, 6 Ed, 1925, Shaw and Sons, London
- 11 BRACHMAN, D S Auricular fibrillation, *Lancet*, 1921, i, 374
- 12 MOHLER, H K, and LINTGEN, C Auricular fibrillation, *Penn Med Jr*, 1931, xxxv, 68
- 13 CAMPBELL, M The etiology of auricular fibrillation, *Guy s Hosp Rep*, 1929, lxxix, 261
- 14 LEVINE, S A Auricular fibrillation some clinical considerations, *Am Jr Med Sci*, 1917, cliv, 43
- 15 WHITE, P D Observations on functional disorders of the heart, *Am Heart Jr*, 1926, i, 527
- 16 MCEACHERN, D, and BAUER, B M Auricular fibrillation, *Am Jr Med Sci*, 1932, clxxxiii, 35
- 17 LEVINE, S A, and FULTON, M N The relation of hypertension to mitral stenosis, *Am Jr Med Sci*, 1928, clxxvi, 465
- 18 COFFEN, T H The favorable prognosis of auricular fibrillation, *Jr Am Med Assoc*, 1923, lxxxi, 440
- 19 LAWS, C L, and LEVINE, S A Clinical notes on rheumatic heart disease with special reference to the cause of death, *Am Jr Med Sci*, 1933, clxxxvi, 833
- 20 STROUD, W D, LAPLACE, L B, and REISINGER, J A The etiology, prognosis, and treatment of auricular fibrillation, *Am Jr Med Sci*, 1932, clxxxiii, 48
- 21 YATTE, W M Pathologic changes in auricular fibrillation and in allied arrhythmias, *Arch Int Med*, 1929, lviii, 808
- 22 LEVIN, L Auricular fibrillation prognostic criteria, *Jr Med Soc N J*, 1930, xxxii, 514

THE ETIOLOGY OF ABDOMINAL PAIN IN DIABETIC ACIDOSIS¹

By HARRY WALKER, M D , *Richmond, Virginia*

THE usual signs, symptoms, and laboratory findings in prediabetic coma are well known. The clinical picture of dehydration associated with malnutrition, polyuria, and odor of acetone on the breath, decreased intraocular tension, and Kussmaul breathing, when found in conjunction with sugar and acetone bodies in the urine make a clinical picture that could hardly be confused with any other condition. Other laboratory findings are a high blood sugar, a low CO₂ combining power of the blood plasma, and leukocytosis. The white cell count sometimes rises above 65,000¹ per cubic millimeter of blood.

This picture is usually clear cut and offers no difficulty in diagnosis. There are, however, exceptions to this rule, in fact, the picture is occasionally complicated by symptoms and signs referable to the abdomen which may make it difficult or impossible to determine whether the patient has an intra-abdominal surgical lesion, or whether the symptom complex from which the patient is suffering is due entirely to acidosis. Obviously, it is of primary importance promptly to make a differential diagnosis. To subject a patient on the verge of diabetic coma to an emergency surgical operation is never wise unless a true emergency exists, on the other hand, to delay too long an operation in a diabetic that needs emergency surgery is equally unwise.

The following is a case report of this complex syndrome, presenting an excellent example of the difficulty in diagnosis that some of these patients present when first seen.

CASE REPORT

J. B., male, aged 17, admitted to Memorial Hospital March 25, 1933.

The patient, a known diabetic for two years, was discharged from this hospital on November 10, 1932, following treatment for an early diabetic coma. At the time of his dismissal the patient was placed on a diet with 225 grams of carbohydrate, 80 grams of protein, and 60 grams of fat together with 20 units of insulin three times a day before meals. The patient progressed well on this treatment and was followed in the Out-Patient Department weekly. He followed his instructions faithfully until seven days before admission. At this time his supply of insulin became low and he took only 15 units each day instead of his usual 60 units. On the day before admission he did not eat as much as usual and took only 10 units of insulin, before breakfast. On the day of admission he ate practically nothing. The patient went to bed feeling very well but awoke in the early part of the night (about 1 00 a m.) nauseated. He continued to be nauseated throughout the night but did not vomit until the following morning at about 8 00 a m. He continued to vomit throughout the day, vomiting every five to 10 minutes. After each attack of vomiting the

* Received for publication October 21, 1935.

From the Department of Medicine, Medical College of Virginia.

patient would drink a large quantity of water. About 1 00 p m the patient began having a sharp pain in the epigastrium just to the left of the mid-line. The pain increased in severity, was sharp and shooting in character, soon extending over the entire abdomen and radiating up the chest as high as the supra-sternal notch. The pain was increased by deep respiration. Nausea, vomiting, and constant pain continued, all increasing in severity. At about 4 00 p m the patient's mother gave him 40 units of insulin which seemed to have no effect on either the vomiting or pain. All during the day and the night before the patient had passed large amounts of urine, much more than usual. At 6 00 p m the patient was admitted to the hospital.

Physical examination at that time revealed a much dehydrated white boy in agonizing pain. The respiration was shallow. Examination of the head and neck showed nothing unusual. The heart rate was 100 and the blood pressure 120 mm of mercury systolic and 80 diastolic. There was no evidence of cardiac enlargement and no murmurs were present. The lungs were clear. The abdomen was rigid, board-like in character, giving one the impression that one was dealing with a perforated peptic ulcer or some other emergency surgical condition. There was a slight infection of the terminal phalanx of the left thumb. The remainder of the examination was negative.

The laboratory reports were as follows: Urine, amber, clear, acid, specific gravity 1.025, heavy trace of albumin, sugar four plus, acetone four plus, diacetic acid two plus. Red blood count 5,160,000, hemoglobin 95 per cent, white blood count 26,600, 87 per cent polymorphonuclears, 11 per cent lymphocytes, and 2 per cent eosinophiles. The blood sugar was 444, and the plasma CO_2 was 20.2 volumes per cent.

Immediately after admission the patient was given 50 units of insulin, hypodermically, and 1,000 c c of normal saline were given by vein. The abdominal pain immediately began to lessen in severity and within 45 minutes the pain had completely subsided and the abdomen had become soft. At this time the blood sugar was repeated and was found to be 380 mg per 100 c c of blood, the CO_2 was 22, the urine was still positive for sugar, acetone, and diacetic acid.

Confronted with a situation of this kind, how can a differential diagnosis be made? The answer cannot be given without making qualifications. Literature concerning this condition is scarce, however, McKittrick² in a somewhat recent review suggests the following observations as useful. First, he (McKittrick) states in his review of patients who had been operated on and no surgical lesion found, that these patients before operation always suggested some wide-spread abdominal pathologic process as the cause of the abdominal findings. Second, that in diabetic coma, vomiting usually precedes pain, while in pre-coma cases with surgical complications, pain usually precedes vomiting—particularly is this true in acute appendicitis. Third, when appropriate therapy is applied, the signs and symptoms due to acidosis clear up promptly, while, of course, the signs and symptoms in the surgical cases will usually progress. He further states that differentiation is not always possible and, when the patient does not respond in a reasonable length of time, an exploratory laparotomy should be done.

The etiology of this interesting condition has never been satisfactorily explained. Various possibilities, of course, have been suggested and explored. Dilatation of the stomach has been offered as a possible cause, but it is common knowledge that gastric dilatation does not produce a true spasm of the abdominal muscles. It, of course, does produce discomfort

in the abdomen, but rarely if ever agonizing pain. Hepatic engorgement has also been suggested as an explanation, but here again engorgement of the liver as we see it clinically never produces a syndrome comparable to that seen in the case reported here. That the abdominal symptoms in diabetic acidosis could be due to a surgical lesion is ruled out by the fact that recovery is too prompt. In addition to this fact, exploration fails to find sufficient incriminating evidence against any abdominal organ to account for the clinical findings, and the same may be said of autopsy findings in these cases. Neither does dehydration explain all of the facts since it is a routine finding in pre-coma cases, and yet, certainly the majority of even markedly dehydrated patients present no abdominal signs or symptoms. Then again dehydration when found in other clinical conditions does not produce the findings reported here.

It is always dangerous to draw conclusions from one case, yet, in the case history here reported several things stand out. First, the vomiting preceded the pain by several hours, second, the patient received insulin in large amounts before entering the hospital, yet, in an insufficient quantity to control the acidosis, third, prompt relief followed the administration of a small quantity of normal physiological salt solution, fourth, the patient continued to show evidence of acidosis after the pain had subsided. These facts suggest that acidosis was not solely responsible for the symptoms since, when measured by laboratory means, there was no reduction. The history suggests too that insulin was certainly not the sole factor in controlling the symptoms in this case, but rather that the salt solution was responsible for the relief of symptoms. When one thinks of other clinical conditions such as heat cramps and "gastric tetany," the connection seems even more probable.

Heat cramps, a condition described by Edsall,³ is commonly seen in the South, especially in the summer months in those who do manual labor while exposed to the sun or high temperatures. It is well established that this condition is in some way associated with chloride deficiency and is brought about by loss of chlorides, chiefly through perspiration. Salt solution not only promptly controls the symptoms but prevents them. It might be added that the pain in this condition is so severe that it does not readily yield to moderate, or for that matter, sometimes even to large doses of morphine sulphate.

A review of some of the facts known about "gastric tetany" associated with pyloric obstruction makes this explanation even more plausible. Here the patient loses his chlorides by vomiting and not only does abdominal pain follow but so does violent pain in any group of muscles that are vigorously exercised. In view of these facts, it is suggested that the chain of events producing abdominal symptoms in diabetic acidosis probably develops in this order. First, because of improper fat oxidation, acidosis develops, the acidosis in susceptible patients causes vomiting, the acidosis not being controlled, the vomiting continues. Second, the continuous vomiting depletes

the body of chlorides because of loss of hydrochloric acid. The excessive diuresis would produce further chloride loss. Third, in the exercise of abdominal muscles and muscles of respiration, there is brought about a condition in these muscles similar to that which is present in heat cramps and "gastric tetany", hence, the pain, and hence the relief by sodium chloride.

It is regretted that no blood chloride determinations were made on this patient. However, it must be remembered that, when marked dehydration of the body is present, a determination of the plasma chlorides is not a true index of the total body chlorides. In fact, plasma chlorides may remain normal while the chloride content of the body as a whole may be markedly reduced. The chlorides in "gastric tetany," of course, are always low but in heat cramps this is not the case. In fact, chloride determinations were made on the blood plasma of eight patients admitted to our medical wards during the past summer, and in only two of them were the chlorides decreased and in those very slightly. That there is certainly depletion of the body chlorides in diabetic acidosis is a known fact. Peters and Van Slyke⁴ state that the depletion may be brought about in several ways, namely, vomiting, diuresis, and the displacement of chlorine by oxybutyrate anions, the displaced chlorine being excreted as ammonium chloride. Certainly, if this patient's plasma chlorides had been normal, it would not have thrown any light on the total body chlorides and would be no argument against the explanation for his pain given here.

CONCLUSIONS

A patient with diabetic acidosis and associated abdominal symptoms is reported. A review of the history and the prompt relief which followed the administration of sodium chloride suggest that the abdominal pain present in this condition may be associated with depletion of body chlorides.

BIBLIOGRAPHY

- 1 ALIAN, F. N. Diabetic acidosis and leukocytosis, *Am Jr Med Sci*, 1923, **vii**, 641-645
- 2 MCKITTRICK, L. S. Abdominal symptoms with and without abdominal lesions in diabetic acidosis, *New Eng Jr Med*, 1933, **cciv**, 1033-1036
- 3 EDSALL, D. L. Two cases of violent but transitory myokymia and myotonia apparently due to excessive hot weather, *Am Jr Med Sci*, **cxxvii**, 1904, 1003-1011
- 4 PETERS, J. P., and VAN SLYKE, D. D. Quantitative clinical chemistry, I, 1931, The Williams and Wilkins Co., 1054-1055

INTENSIVE LIVER THERAPY IN SPRUE *

By PHILIP CORR, M D , F A C P , *Riverside, California*

A recent report by Rhoads and Miller¹ indicates that adequate liver therapy is as satisfactory in sprue as it is in the somewhat related condition of pernicious anemia. These excellent results with liver therapy have stimulated an increase in the recognition of nontropical cases of sprue which are often reported as cases of chronic idiopathic steatorrhea. Mackie,² in July 1933, was able to find only 28 unquestioned cases of nontropical sprue and he added one of his own. Increased recognition of cases is evidenced by the fact that by March 1935 Snell³ was able to state that there were well over 100 nontropical sprue cases on record. He further stated that 15 cases had been seen at the Mayo Clinic since 1927 with about half of them having been studied during the previous year.

The diagnosis of sprue is made on the basis of finding excess fat in the stools after a history is obtained of gaseous indigestion with marked loss of weight and weakness associated with chronic recurring diarrhea of watery, bulky stools. Intermittent sore mouth and tongue, latent or active tetany, amenorrhea, and an inanition edema are common symptoms in the more advanced cases. Emaciation with a distended abdomen is often striking. Laboratory findings, in addition to the excess fat seen macroscopically and microscopically in the pale, voluminous, foul stools, include the finding of a hypochromic or macrocytic anemia, hypocalcemia, and a decrease in the serum proteins. The roentgenologic findings include osteoporosis and osteomalacia in the advanced cases. Dilatation and redundancy of the colon have been commonly observed. Recently Camp⁴ has described dilatation of the duodenum and a smoothing out of the irregular shadows of the valvulae conniventes and a clumping of the barium in smooth sausage-like masses in the jejunum and ileum.

Pancreatogenic steatorrhea differs from the steatorrhea of sprue in that the fault is in the decrease or lack of the external pancreatic secretion, and there is no fault in the absorptive power of the intestine. A much higher azotorrhea may be observed in pancreatic disease⁵. The frequently associated diabetes and the lack of concomitant sprue symptoms resulting from faulty absorption and atony of the intestines usually point to the correct diagnosis of pancreatic difficulty.

Pernicious anemia is characterized by lack of intrinsic factor⁶ with the resultant principal effect upon the hematopoietic system without prominent bowel physiology disturbance. The rather constant presence of free hydrochloric acid in the gastric contents in sprue is a distinct aid in the differential diagnosis.

Pellagra is differentiated at times with great difficulty particularly in the

* Received for publication October 10, 1935

early cases. The skin lesions and the mental symptoms are particularly helpful in the diagnosis of pellagra. Fortunately the treatment in the two conditions is about the same.⁷

The etiology of sprue is debatable but all students agree that there is a dietary deficiency factor. It is generally felt that in spite of Ashford's⁸ work *Mompha albicans* is usually only a secondary invader² which causes much of the frothiness of the stool so often described in tropical cases. This dietary deficiency consists in a lack of an extrinsic factor in the food closely associated, if not identical, with the extrinsic factor of Castle. This lack, perhaps associated with a deficiency or lack of the intrinsic factor in some cases,⁹ brings about the pathology in the small bowel which interferes with the absorption of the hematopoietic substance, fats, and to a lesser extent other food elements.

There is no agreement about a characteristic underlying pathology. Marked reduction to complete absence of fat in the body and a liver considerably reduced in size are the constant evidences of starvation. Reduction in the size of the heart is common from the same cause. It has been felt that the essential lesion is an atrophic enteritis with patchy, transient, inflammatory lesions not always present at autopsy.¹⁰ This may account for the widely divergent autopsy findings noted in the gastrointestinal tract in sprue. Fatal perforation has occurred in the cecum from thinning of the wall.¹¹ A gastro-jejuno-colic fistula has caused sprue-like symptoms,¹² but an extensive chronic ulcerative enteritis seen one year ago did not have sprue-like symptoms.¹³ The most careful work on the bone marrow evidences that sprue in this respect simulates pernicious anemia.¹⁴ Roentgenologic evidence indicates that there is an edema as well as atony in the intestinal tract.³

Manson-Bahr¹⁵ was perhaps wise in saying that nontropical sprue cases in order to be diagnosed as such should present the typical diarrhea, flatulency, anemia, mouth symptoms and the characteristic response to appropriate treatment.

The following recently observed typical case of sprue is presented as a basis for emphasis of many of the interesting features of this symptom syndrome, particularly as to its treatment.

CASE REPORT

History. K. K., an American woman aged 49 years for 12 years a resident of Havana, Cuba, was first seen in consultation with Dr. Bon O. Adams, March 29, 1935. Except for an increasing lassitude which had been present since 1925 she was active and in good health until January 1932 when, for the lassitude, she had all her teeth removed. Sore mouth followed and was present intermittently since the alveolectomy. The sore mouth was troublesome enough for her to get three complete sets of dentures without lasting satisfaction from any of them. Anorexia had been prominent and persistent since the onset of the sore mouth and tongue. The weight dropped from 135 pounds in January 1932 to 69 pounds in November 1934. Since November she had not been weighed, but an increasing edema, which had been transiently present several months before, had increased her weight to a probable 110 or more pounds. Weakness had become so severe that she could barely turn

over in bed unaided. Since the onset of her trouble in 1932 she had a painless, watery, bulky but not foamy diarrhea with passage on an average of three to four stools daily, the number varying from one to nine. Usually there would be three or four stools early in the morning and occasionally a stool before meals when there was an exacerbation. In spite of this copious diarrhea the gaseous distention was so marked that enemas were required twice daily to keep her comfortable. The menses had ceased in 1931 when the patient was 45 years of age. Intermittent and rather marked tingling of the finger tips had been noted for several months.

For a period of 10 months before November 1934 the patient had been carefully and competently studied in the middle west. No diagnosis had been made, but the letters of information she carried with her evidenced that anorexia nervosa was considered to be the most likely explanation of her difficulties. During their observation the hemoglobin dropped from 89 to 50 per cent and the erythrocytes dropped from 3,200,000 to 2,010,000 in spite of temporary improvement from blood transfusions. The leukocytes had dropped from 6,500 with 47 per cent neutrophils, to 3,100 with 47 per cent neutrophils. This macrocytic anemia was accompanied by 13° of free hydrochloric acid in the gastric contents. Stools for blood, parasites and ova, a Kahn test, a basal metabolic rate, liver function tests using both the galactose tolerance and the dye methods, and repeated roentgenologic gastrointestinal examinations were reported as normal. Their therapy had included forced feeding to overcome the effects of previous inadequate protein intake, and a period of intramuscular liver extract therapy which failed to bring about satisfactory hematopoietic response. For some months the patient had been taking six capsules of liver extract (Extralín) and pancreatic extract (Pankreon).

Examination revealed extreme weakness with an extreme degree of edema of the legs and of the abdominal wall, with moderate edema of the arms and face. Fluid was definitely present in the abdomen. The blood pressure was 78/62 with a pulse of 80 and a temperature of 97.8°. The tongue was pinkish-red and atrophic with almost complete absence of papillae. Trousseau's sign was definitely positive.

The stools contained an excessive amount of fat macroscopically and microscopically. Cultures of two stools failed to grow *Monilia*. The hemoglobin was 43 per cent (Sahli) with 1,330,000 red blood cells and a color index of 1.6. The leukocytes numbered 3,000 with 51 per cent neutrophils. The urine contained a trace of albumin. The blood urea was 10 mg per 100 cc.

On the basis of this typical history and the confirmatory findings, a diagnosis of sprue was made. It was felt that previous liver therapy had been inadequate. Beginning April 1, 1935 daily intravenous injections of 20 cc of liver extract (Parke-Davis & Co.) were given for 12 days. This was followed by 16 similar injections given every second day, following which the intervals between injections were gradually lengthened. By September they were being given twice monthly.

The diarrhea promptly stopped after the first injection of liver extract, but for five days there was no other sign of improvement, the patient appearing almost moribund. Severe tetany developed after giving pitressin to relieve the gaseous distress in the abdomen. The use of the tourniquet for the intravenous therapy consistently produced annoying, typical carpal spasms. The blood calcium on April 9 was 7.5 mg and the blood phosphorus 3.5 mg per 100 cc.

Beginning with the sixth day of treatment, improvement in the general condition was dramatic and continuous. By the twelfth day the appetite was ravenous, the patient could sit up in bed with energy to spare, the gaseous distention was much improved, and the tetany had almost disappeared. Vitamin D and calcium was started a few days after improvement in the tetany had begun. The weight was 63 pounds after two weeks of excessive eating but by that time the edema had practically disappeared. Subsequently there was a steady increase in weight so that by September the weight had reached a level at 120 pounds. The sore mouth disap-

Physical examination revealed no changes since the previous entry. The urine was now free from albumin and blood. The basal metabolic rate was still low (minus 26 per cent). A dextrose tolerance test showed a fasting blood sugar of 81 mg per 100 c.c., rising to 112 mg one hour after ingestion of dextrose and receding to 101 mg in two hours, to 99 mg in three hours, and to 94 mg in four hours. Blood calcium was 10.7 mg, phosphorus 3.7 mg, phosphatase 97 units. She was discharged with instructions to resume treatment with ephedrine.

The third hospital entry was in September 1935. She had stopped taking ephedrine two and one-half months before because it was no longer effective. She had reverted to her previous state with the attacks as frequent as before. There was no change in the physical examination. Inhalation of benzedrine sulphate was begun. On the following day she had only one attack of somnolence and the day after that none at all. On the third day the drug was given orally in tablet form, 10 mg three times a day, and, although there were no attacks on that and the following day, she believed that inhalation was superior to the tablets. She was discharged with instructions to continue treatment by inhalation. About a month later she was advised to try the tablets again and to report after two weeks of treatment. She took 10 mg three times a day and in a letter wrote that "they were much more effective than the inhaler. I did not fall asleep once all day while I was taking the pills." She was then advised to omit the treatment to note whether the complaint would return. The following report was received: The attacks "started again two days after I stopped taking [the tablets]. Upon resuming the treatment I was able to stay awake from 6.30 in the morning until 10 or 11 o'clock at night."

Case 4 R. R., an American bank clerk, aged 32, entered the hospital complaining of falling asleep in the daytime. The illness had begun insidiously about 15 years ago. At first, he could control the attacks by force of will, but the degree of somnolence had increased gradually until recently he could not control it at all. It was especially troublesome during any monotonous action, such as signing checks or riding in a train. He slept poorly at night, and had frequent unpleasant dreams. An attack lasted only a few seconds. Whatever he was doing (talking, riding or driving an automobile) he often carried on automatically during an attack. He had had two narrow escapes from accidents while driving an automobile. The tendency to sleep was worse after meals and in the middle of the afternoon. The sleep was not deep and sometimes merely a sort of semi-consciousness. He responded when spoken to and was easily aroused. There were no prodromal symptoms or after effects except anger at having been unable to prevent an attack. Hearty laughter and violent anger have produced slight cataplectic symptoms consisting of fluttering of the eyelids and a momentary weakness of the legs followed by twitching. They have been much less frequent during recent years. Nocturnal sleep was poor and often disturbed by vivid and sometimes unpleasant dreams. A year before, he had had thyroid and pituitary medication without benefit.

The family history revealed that his father had hay fever. Both parents had died of kidney trouble at age 50. There were no siblings. He was married and had four living and well children. There had been one miscarriage. During the last three years his sexual life had been unsatisfactory, apparently because his wife objected to other pregnancies. He had had measles, mumps, chicken-pox, whooping cough and scarlet fever as a child and malaria 20 to 25 years ago. The highest weight, that on admission, was 140 pounds.

Physical examination revealed abdominal obesity. The heart and lungs were normal. The systolic blood pressure was 130 mm mercury, the diastolic 78 mm. The pulse rate was 88 per minute. He wore glasses for astigmatism. The pupils were not round. The fundi were normal. He was observed during a narcoleptic attack which he induced by reading. The sleep appeared normal, he snored heavily. Respirations were 15 per minute. The eyeballs were not rolled upward, but had a

tendency to wander. The pupils were very small. Attempts to elicit the reflexes aroused him. He answered a few questions in a normal manner and then again fell into a deep sleep.

The urine contained a very slight trace of albumin, but was otherwise normal. The blood count was normal. The non-protein nitrogen of the blood was 28 mg, uric acid 3.7 mg, sugar 96 mg, calcium 10.7 mg, phosphorus 2.9 mg, and cholesterol 190 mg in 100 c.c. The Wassermann and Kahn tests were negative. The basal metabolic rate was minus 14 per cent, the galactose tolerance was slightly diminished. Roentgen-ray examinations. The skull plates showed expansion of the diploë with hyperpneumatization of the sinuses and beginning sclerosis of the vault. There was calcification of the pineal gland. The sella turcica measured 7 by 12 mm, and was regular in outline. Dextrose tolerance test. Fasting 100 mg, one-half hour after dextrose, 191 mg, one hour, 200 mg, two hours, 193 mg, three hours, 129 mg, four hours, 75 mg, five hours, 71 mg, six hours, 90 mg.

He was discharged with instructions to use benzedrine by inhalation. He reported later that the treatment produced no appreciable effect. Oral treatment, 10 mg three times a day, was then begun. The attacks were completely controlled. At present, after several weeks of continuous medication, he is free from symptoms, except some drowsiness while riding on a train. He sleeps well at night and is not troubled by unusual dreams. At first, he had had an occasional slight feeling of nausea when he took the tablets without water, but that is no longer troublesome.

Case 5. P. S., a colored girl, aged 12½ years, complained of frequent attacks of sleeping. There was a history of a fall at age four which her mother believed to have been responsible for the illness, although there had been no immediate ill effect. She had not been unconscious. The diurnal naps became particularly noticeable when she entered school. The teacher reported that the child went to sleep during class hours. Her mother stated, however, that she had taken long daily naps before that. The tendency to somnolence was more pronounced on hot days, but there was no predilection for a special time of the day. It occurred only when she was quiet or performing a monotonous task (knitting) and never while she was at play or when something was holding her interest. The duration of the attacks was usually an hour or two. She was easily aroused but went to sleep again if permitted to do so. She did not continue to perform previously begun actions during an attack. Cataplectic symptoms had not been noted, but at times she twitched while asleep. Treatment with thyroid, prescribed elsewhere, had been without benefit.

The family history was not relevant. Birth and infancy had been normal. She had had measles, mumps, chicken-pox, pertussis and scarlet fever. Frontal headaches were frequent, especially in hot weather. Occasionally there was tinnitus in the right ear. Her feet swelled and were cold during cold weather. Constipation was controlled by the regular use of mineral oil. Menstruation had begun six months before and had been normal except for dysmenorrhea on the first day. She tired easily, was slightly nervous and very irritable. She slept well and was not troubled abnormally with dreams. The highest weight, that on admission, was 95 pounds. Physical examination revealed nothing abnormal except flat and pronated feet which an orthopedic consultant believed to be congenital.

The urine was normal. Blood. The hemoglobin was 12 to 14 grams per 100 c.c. (74 to 78 per cent), erythrocytes numbered 3,570,000 to 3,970,000 per cu. mm., leukocytes 8,500 to 9,700, of which 12 to 21 per cent were eosinophiles. The non-protein nitrogen was 26 mg, uric acid 2.8 mg, sugar 80 mg and cholesterol 202 mg in 100 c.c. blood. Feces. No ova or parasites were found. Dextrose tolerance test. The fasting blood sugar was 83 mg, one hour after dextrose it was 141 mg, in two hours it was 121 mg, in three hours, 115 mg, in four hours, 112 mg, in five hours, 83 mg, and in six hours, 93 mg. The basal metabolic rate was minus 23 per cent. The galactose tolerance was moderately diminished. Roentgen-ray examinations.

The skull was normal, the sella measured 6 by 12 mm and was regular in outline. The sinuses were normal. Cerebrospinal fluid. Manometric readings were normal, cells numbered 1 per cu mm, the sugar content was normal, globulin not increased, the colloidal gold and Wassermann tests were negative.

Benzedrine sulphate, 10 mg three times a day, was prescribed. It gave marked relief, but some degree of somnolence still occurred at the end of the morning and toward evening. The amounts of the drug taken in the morning and at noon were then increased to 20 mg each, the evening dose remaining at 10 mg. Since then she has been free from attacks throughout the day, except slight drowsiness in late afternoon. Her mother reports that she appears normal in every way but that the increased medication induced an additional menstrual period (3 periods in 1 month). An occasional feeling of fullness at meals, not noticed before, has been present during the past two weeks.

Case 6 W L, a Nova Scotian farmer, aged 22, complained of "falling asleep in the middle of the day's work." The illness began about six years ago with what he described as "a breakdown in health," consisting of nocturnal insomnia, nervousness, excitability and increased drowsiness in school. He stated that before that time he was well, but more searching questioning elicited the information that he had had mild attacks of sleepiness in school during the preceding year or two.

Recently the attacks of diurnal sleep, about four or five a day, have lasted from a few seconds to several minutes. They have occurred at any time of the day. He has been easily aroused but has been irritated thereby. If he awoke spontaneously, he felt refreshed. A warm room, monotonous procedure and inactivity favored the onset of an attack. Automatic action was frequent. He slept poorly and had unpleasant dreams about being pursued by animals. Excitement, anger, or hearty laughter often caused his muscles to relax, "they would not do what I wanted them to do." During these cataplectic spells he was unable to speak but remained conscious. Their duration was but a few seconds. He believed that they were less frequent than they had been at the beginning of the illness. Sedative medication for insomnia has been used. Constipation has been marked and began just before the onset of the narcolepsy. He has had frontal headache for several years when he strains his eyes (reading, watching motion pictures). There has been a gain of 30 pounds in weight during the past six years. The weight at examination was 190 pounds.

Physical examination revealed nothing remarkable. He had the appearance of an exceptionally rugged youth, large of frame and only moderately obese.

The urine was normal. The blood count showed a mild eosinophilia (8 to 9 per cent) but was otherwise normal. Chemical and serological examinations of the blood were normal. The basal metabolic rate was plus 4 per cent in the first test, and minus 15 per cent and minus 20 per cent in two subsequent examinations. Roentgen-ray examination of the skull showed expansion of the diploe and hypopneumatization of the sinuses. The sella turcica measured 5 by 8 mm and was regular in outline. The heart and lungs were normal.

Inhalation of benzedrine sulphate was used for two days and gave slight relief. Oral medication, 10 mg three times a day, has been followed by marked improvement, although there is still some drowsiness when he is inactive. He states that he can now read for several hours at a time, whereas before treatment was begun he fell asleep a few minutes after beginning to read. Insomnia is much less troublesome, but he still has occasional unpleasant dreams.

SUMMARY

Our experience with narcolepsy supports the statement that the disease may occur at any age and that in the majority of cases it begins before age

Tabular Summary of Important Findings in Six Cases of Narcolepsy

Case Sex, Age	Narcolepsy						Cataplexy		Treatment				Miscellaneous Findings				
	Age of Onset	Dura- tion in Years	Length of Attacks	Aggravation	Pro- dromes	Automatic Actions	Length of Attacks	Exciting Cause	Ephedrine	Benzedrine			B M R	Dreams	Irrita- bility	Obesity	Constipation
										Inhal- tion	Orally	Toxicity					
I M F 52	49	3	Few seconds to several minutes	Monotony after meals, morning cold days, very warm room	Diplopia and dull feeling in eyes	At times	Few seconds or minutes	Hearty laughter, excitement	Slight relief	Not used	Complete relief	Possibly aggravation of existing gastric symptoms at first	-24%	Unpleasant, insomnia (relieved by treatment)	Yes	Moderate, especially since onset of narcolepsy	No
II O L B 17	10	7	Up to 1 hour at first, now only a few minutes	Monotony, warmth, fatigue	None	Writing, walking (has lost his way)	Few moments (none for 6 months, fre- quent at first)	Excitement laughter	No relief	Not used	Complete relief	Anorexia for first few days	-21%	Many, some of them horrible less troubled in last year No insomnia	Yes	Obese before tall since onset	No
III A H 16	10	6	10-20 min utes	Monotony, forenoon	None	Walking rarely	5-20 minutes	Hearty laughter, anger, fear	Moderate relief at first, later none	Moder- ate relief	Complete relief	None	-16% -22% -26%	"Horrible" at first, less recently	Rare	Gradual gain since onset of narcolepsy	Moderate
IV R R. 32	17	15	Few seconds to several minutes	Monotony inaction, warmth, 11 a m -2 p m., after supper	Momen- tary cloud in front of eyes	Frequent Writing, driving, talking	Momentary (rare slight attacks)	Hearty laughter, sudden anger excitement	No relief	No relief	Marked but not complete relief	Occasional slight nausea at first taking tablets without water	-11%	Unpleasant, insomnia (relieved by medicines)	No	Slight	No
V P S 12½	4(?)	8(±)	Few minutes to several hours	Monotony, warmth, inaction	None	None	No cataplectic seizures		Not used	Slight relief	Almost complete relief with 50 mg	Added menses, feeling of fullness with meals	-23%	Not abnormal Sleeps well	Marked	None	Marked
VI W L 22	14-15	7-8	Few seconds, rarely a few minutes	Monotony, warmth, afternoon	None	Walking frequently, other ac- tion rarely	Few seconds	Excitement, sudden anger, hearty laughter	Not used	Slight relief	Marked but not complete relief	None	+ 4% - 15% - 20%	Unpleasant, insomnia	Only when aroused	Moderate	Very marked began just before onset of narcolepsy

twenty-five All of our patients are especially prone to become sleepy under monotonous actions or influences The early part of the day is particularly conducive to drowsiness in two of our cases, in two there is a post-prandial inclination, and one patient is more susceptible in the afternoon In two cases there is no predilection as to time of day Warm weather or a warm room is a factor in three cases Two show no seasonal influence and one, contrary to general observation, is worse on cold days Unpleasant dreams are recorded by four of the patients Cataplectic seizures are present in five cases, but not in case 5, the youngest of the series The basal metabolic rate in all of our cases is lower than the mean rate in the large series reported by Daniels³ The reason for this is not apparent

Oral treatment with benzedrine sulphate has been followed by marked relief in all cases of our series The effective daily amount of drug varied from 20 to 50 mg Inhalation was tried in four cases, with slight benefit in case 5, moderate in cases 3 and 6, and none in case 4 It appears that the difference between inhalation and ingestion is quantitative One patient complained of slight nausea at the beginning of oral medication, another's gastrointestinal symptoms were aggravated during the first period of treatment, but not subsequently, and a third had slight temporary anorexia at the beginning of each period of treatment One patient, a colored girl, aged 12½, had an additional menstrual period while taking 50 mg of the drug and has complained recently of a slight feeling of fullness at mealtime

BIBLIOGRAPHY

- 1 New and Non-Official Remedies, 1935
- 2 PRINZMETAL, M, and BLOOMBERG, W The use of benzedrine for the treatment of narcolepsy, *Jr Am Med Assoc*, 1935, cv, 2051
- 3 DANIELS, L E Narcolepsy, *Medicine*, 1934, xiii, 1
- 4 TROMNER, E Narkolepsie (Schlafzwang), *Zentralbl f d ges Neurol u Psychiat*, 1929-30, liv, 326
- 5 ROSENTHAL, C Zur Pathogenese, Aetiologie und versorgungsrechtlichen Bedeutung der "genuinen" und post-traumatischen echten Narkolepsie, *Arch f Psychiat*, 1932, xvi, 572
- 6 GOLDFLAM, S Zur Frage der genuinen Narkolepsie und ähnlichen Zustände, *Deutsch Ztschr f Nervenheilk*, 1924, lxxii, 20
- 7 GRUN, R Beitrag zur Kenntnis der Narkolepsie und der Frage der Dienstbeschädigung bei dieser Krankheit, *Ztschr f d ges Neurol u Psychiat*, 1931, cxxxiv, 155
- 8 BEYERMANN Über pathologische Schlafzustände, insbesondere narkoleptische Anfälle, in ihrem Zusammenhange mit Funktionsstörungen der Hypophyse, *Ztschr f d ges Neurol u Psychiat*, 1930, cxxviii, 726
- 9 REDLICH, E Die Gelineausche Narkolepsie, *Med Welt*, 1927, i, 1281
- 10 THIELE, R, and BERNHARDT, N Erfahrungen über Narkolepsie, *Zentralbl f d ges Neurol u Psychiat*, 1931, lvi, 143
- 11 JANOTA, O Symptomatische Behandlung der pathologischen Schlafsucht, besonders der Narkolepsie, *Med Klin*, 1931, xxvi, 278
- 12 ALLES, G A The comparative physiologic actions of the di-phenylisopropylamines I Pressor effect, *Jr Pharmacol and Exper Therap*, 1933, lvi, 339

ABDOMINAL DISTENTION IN LOBAR PNEUMONIA

By JOEL GOLDMAN, M D , and ABRAHAM COHEN, M D , *Philadelphia, Pennsylvania*

IN scanning the literature on meteorism we found a most interesting lecture, written by Francis Sibson¹ in 1873 We wish to quote from this classic

You will at once see how seriously distention of the colon must affect the organs of the chest, not only the lungs, but also the heart, by displacing that organ to the left, whereas, in the case of the stomach, its displacement tended rather to the right

We find that the heart and the lungs are put to an immense disadvantage—that the lungs are compressed and the reserved air driven out of them—that the heart is compressed and the blood driven out of it—that the ventricles are diminished in size and are incapable of receiving so much blood as they did before—that there is an obstacle to their action, and that they are incapable of sending out the blood that they have already received with the ease that they did before,—again, if you look at the walls of the chest and the diaphragm, you see what an obstacle is put to the very limits, by which, as it were, the lungs expand and the heart is moved The cartilages of the ribs are pushed aside and lifted upwards The cage of the chest has reached the limit of its power by the elevation given to it, and permanently given to it by the distention of the abdomen Again look at the diaphragm, lifted up by this immense distention How can it act downwards? If the diaphragm is affected by peritonitis, the inflammation paralyzes the inflamed muscle The whole content is then narrowed to the smallest bounds, and the whole work of respiration must be done by the few ribs remaining unassailed at the top of the chest In cases of peritonitis respiration is what is very well called high The whole of the breathing is performed by the labored lifting up of the upper cartilages, the upper ribs and the clavicles—all the muscles that act—the sternocleid, the scalem, the levators of the ribs and the scapulae, are hard at work, and in spite of that, you see visible in the face that the patient is undergoing chronic asphyxia, and must soon die unless his breathing is relieved

THE ORIGIN OF GASES IN THE INTESTINAL TRACT

We are not concerned here with the ordinary accumulation of gas in the intestinal tract, but with the excessive formation of gas which results in flatulent distention

According to the work of Schoen, McIver, Redfield and Benedict,² the only gases of importance in distention are those which are not readily absorbed, hydrogen, nitrogen and methane Other gases, however, may accumulate in the intestinal tract if their rate of formation exceeds their rate of absorption

Cutting³ believes that the origin of intestinal gas is three-fold (1) decomposition of foodstuffs, (2) diffusion of gas from the blood stream, and (3) swallowed atmospheric air He states that gases are produced

* Received for publication August 12, 1935

From the Pneumonia Wards of the Philadelphia General Hospital

by the action of bacteria on sugars in the lower portion of the small intestine and by the action of bacteria on any residue of cellulose which remains after digestion is complete. Free nitrogen occurs in the blood stream under a pressure of about four-fifths of an atmosphere, while oxygen and carbon dioxide occur in chemical combination. The nitrogen is free to leave the blood stream to replace other gases in the intestines when pressure relationships are favorable, whereas in order for oxygen or carbon dioxide to leave the blood stream, not only must pressure relationships be upset, but also conditions must be favorable for the liberation of these gases from their chemical combinations.

McIver⁵ states that normally the amount of gas in the intestinal lumen is minimal because gases diffuse into the blood stream about as rapidly as they are formed. The presence of distention, however, indicates that formation has outstripped diffusion.

In his paper entitled "Constipation," Spencer⁶ points out that the same laws apply in gas exchange between the blood stream and the intestinal lumen as apply to the gas exchange between tissues and blood, and blood and the pulmonary air. In speaking of flatulence he makes the significant statement that "whenever the condition can be anticipated, measures for precaution will prove more valuable than will measures for relief."

Alvarez⁷ feels that flatulence with abdominal distention can become a serious complication during the course of pneumonia. He states that Boothby so far has had little or no trouble with flatulence in a series of patients with severe pneumonia treated in a chamber containing 50 per cent oxygen because in such an atmosphere more of the nitrogen in the bowel can diffuse out.

Wiggers⁸ agrees with other writers that putrefactive and fermentative changes are of minor importance, compared to disturbances in the diffusion of gases. In addition embarrassment of the circulation results from mechanical interference with the splanchnic circulation or from compression of the heart through the diaphragm.

In summary, these authors believe that gaseous distention depends chiefly upon alterations in the interchange of gases between the gastrointestinal tract and the blood. The normal equilibrium may be affected by disturbances in the toxicity and motility of the gastrointestinal musculature, or by interference with the local circulation from various causes. Fermentative processes and aerophagia may be contributory factors. It has also been suggested that the diminished capacity of the lungs in pneumonia may be in part responsible for the distention which is commonly associated with this disease.

Numerous drugs have been utilized to combat distention, none of which are satisfactory in all cases. Saline cathartics or even hypertonic salt solution (Ori¹⁴) may be helpful. While various opiates have been used extensively, there is still a difference of opinion as to their effect upon the movements and tone of the intestine. Nothnagel¹⁶ concluded that small

doses of morphine increased the tone of the intestine while large amounts decreased it. Uhlmann and Abelin¹⁷ demonstrated that the reverse occurred in etherized rabbits and guinea pigs, and Plant and Miller¹⁹ found that morphine and other alkaloids of opium produced a decided increase in tonicity. Eserine has been used with indifferent success for more than half a century. Pitressin and pituitin stimulate contraction of the smooth muscle, and are sometimes very effective. Choline and acetylcholine have been shown by a number of investigators^{22, 23, 24, 25, 26} to stimulate the gastrointestinal musculature. Others,^{27, 28} however, have not obtained constant or conspicuous results with them.

TREATMENT BY SUCTION SIPHONAGE

In June 1933, Paine, Carlson and Wangensteen⁹ described a form of continuous lavage of the duodenum through a nasal tube which was effective in relieving postoperative distention, nausea and vomiting, and they suggested that this form of therapy be employed following gastric, biliary tract, intestinal, and kidney operations. In our paper it is suggested that a modification of this apparatus be made use of in lobar pneumonia and other conditions accompanied by abdominal distention. Distention is a symptom of decided importance since through its mechanical effects and through the distress and fatigue it causes the patient it may well have a decided effect upon the mortality rate in pneumonia and other febrile diseases. We have found the treatment of distention by rectal suction siphonage safe, inexpensive and simple. The results obtained in a large group of patients with lobar pneumonia at the Philadelphia General Hospital are here presented.

From December 1, 1934, to May 20, 1935, 335 cases of lobar pneumonia (220 men and 115 women) were treated in the special fever wards. This hospital accepts only charity cases for treatment. In most of them the disease was far advanced at the time of admission, and, since they were from the poorer sections of the city, their powers of resistance were not of the best.

Of these 335 cases of lobar pneumonia, 129 or 38.6 per cent were clinically distended (39.5 per cent of the men and 36.5 per cent of the women). The distention was of sufficient degree to necessitate active therapy. In comparison, there were few other complications. Our experience indicates that abdominal distention is by far the most common complication of lobar pneumonia.

In previous years, distention had been treated by various accepted routine procedures. The results obtained were far from satisfactory. This year we have used a combination of the laxative action of saline cathartics with the mechanical action of continuous suction siphonage as described below.

Many of the patients entered the hospital with distention, while others developed it as the disease progressed.

The degrees of distention have been classified as follows Grade 1 or minimal, Grade 2 or moderate, and Grade 3 or marked distention A summary is shown in table 2

Early in the series many patients with Grade 3 distention were selected for treatment by suction siphonage, as the treatment was found to be successful, earlier cases were selected until late in the series nearly all were Grades 1 and 2 As has been discovered by other workers, early distention responds to treatment much more readily than when far advanced Grade 3 cases were, at times, most difficult to deflate and to keep deflated, on the other hand, distention in Grade 1 or 2 cases rarely recurred once they were successfully deflated It was finally decided to start suction siphonage on all cases that showed the earliest signs of distention These were easily controlled, and the deflation was maintained in practically all so treated However, many cases admitted with Grade 3 distention were refractory

TECHNIC OF RECTAL TUBE SUCTION SIPHONAGE

The apparatus used is almost the same as that described by Paine, Cailson, Wagensteen,²⁹ and Paine and Phillips,³⁰ in the treatment of postoperative distention, nausea and vomiting by nasal catheter suction siphonage, with the exception that a soft rubber rectal tube (French²⁸) has been substituted for the Levin duodenal tube (Figure 1)

The patient who has become distended is given cleansing soap suds enemas until the return flow is fairly clear or until a successful return of fecal material has been obtained Usually one or two soap suds enemas are sufficient For a successful deflation the feces must be liquefied since solid stools and hard fecal masses will block the rectal tube A liquid stool is obtained by giving the patient, daily, one ounce of saturated magnesium sulphate solution Once a liquid stool is obtained, the dosage of the saline laxative may be reduced However, in dehydrated patients or in older individuals with fecal impactions, large doses of the drug may be necessary Most of the failures occurred in patients with hard, impacted feces which were resistant to laxative action

A soft rubber rectal tube is inserted from two to three inches into the rectum If the tube is forced any farther into the rectum it will coil on itself, balloon out the rectum and give the patient a false rectal impulse (figures 2 and 3) The tube is lubricated with either vaseline or an astringent rectal jelly The latter is used to allay the slight tenesmus which may appear in those cases which are under treatment for fairly long periods of time The following is a description of the apparatus, quoted from Paine and Phillips³⁰ In our apparatus a rectal tube is used in place of the nasal tube

"The apparatus consists of two bottles with the capacity of four liters each One bottle is hung inverted from an irrigation standard by a canvas sling or bag (or by a wire basket as shown in figure 1) The other bottle

is set on the floor at the foot of the standard. A two-holed rubber stopper with two glass tubes fits into the mouth of the inverted bottle. One of these tubes is short (about four inches long) and the other is longer (about 14 inches long) and extends almost to the bottom of the inverted bottle, that is, to the end which is uppermost as it hangs. A rubber tube connects

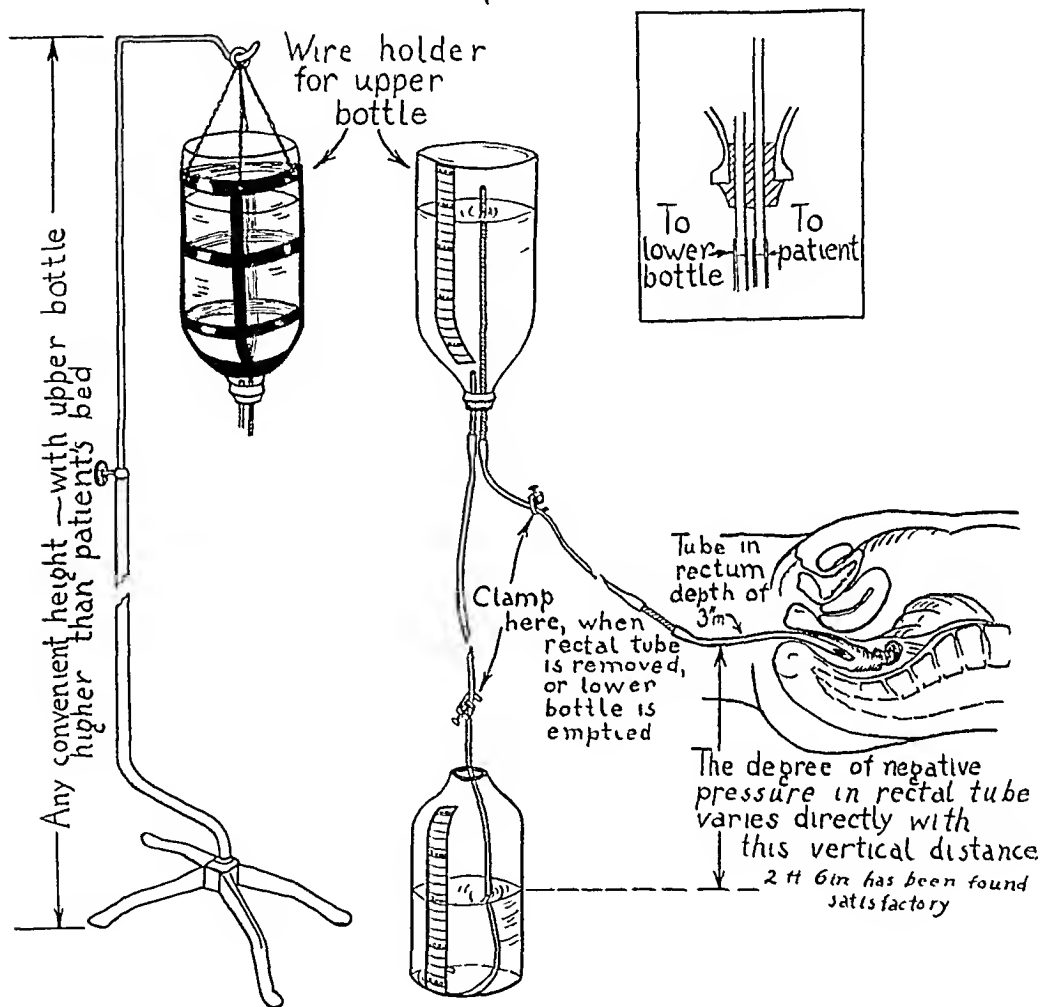


FIG 1

the longer glass to the nasal tube (or rectal tube), and another leads from the shorter glass tube to the bottle which is situated on the floor.

"To start the suction, the upper bottle is filled completely with cold tap water, and the rubber stopper with the tubing attached is put into place in the bottle neck. The rubber tubing leading to the longer glass tube is not yet connected to the nasal tube (rectal tube). Both rubber tubes are clamped off, and the bottle inverted and hung on a standard at a convenient height, about six feet from the floor. The end of the rubber tubing from the shorter glass tube is placed in the floor bottle, and enough water is added

to cover the end of the tube well. This point is very important in order that a closed system will be made and a constant suction insured. The clamps on the rubber tubing are then removed while a finger is held over the end which will later be attached to the nasal tube (rectal tube). If



FIG 2 A rectal tube inserted the wrong way

suction is not immediately felt by the finger there is air in the tubing leading to the lower bottle. This can easily be removed by injecting a few cubic centimeters of water with a syringe into the tube which is connected to the longer glass tube. When suction is perceived, the tube is connected with the nasal tube (rectal tube)."

The return of gas and liquid feces is not measured for there is no

danger of dehydration as long as the urinary output is sufficiently high (from 800 to 1200 c c daily)

The rectal tube and the connecting rubber tubes are irrigated at least every four hours by forcing fluid through them with a syringe. If the



FIG 3 A rectal tube inserted the right way

tubes are blocked by fecal masses they must be thoroughly cleaned or replaced. The apparatus is sterilized by boiling when it is no longer in use.

The rectal tube is used only as long as is necessary to reduce the distention. If it is used excessively long there may be rectal irritation. If distention recurs it may be necessary to repeat the procedure. The continuous use of this method was not insisted upon. If the patient desired a

bed pan it was given to him. From time to time enemas were given. The criticism may logically be offered that the enemas may have relieved the distention, but we have seen hundreds of cases in which they did not.

Pituitrin was found to be nearly ineffectual in stimulating peristalsis in these cases, but Pitressin did help occasionally. No other drugs were used to assist in combating the distention.

The only untoward effect noted after the prolonged use of the rectal tube was tenesmus. This occurred chiefly in those patients who had previously existing internal hemorrhoids, and was easily alleviated by the use of an anesthetic astringent rectal jelly. No rectal bleeding was noted.

The above described procedure has been very successful in combating the abdominal distention of lobar pneumonia. We are presenting the results of such treatment in 100 unselected cases. The following table summarizes the duration of the lobar pneumonia when treatment was first instituted.

TABLE I

12 to 24 hours	2 to 4 days	4 to 6 days	Longer than 6 days
12 cases	23 cases	25 cases	40 cases

It will be noted that 65 per cent of these cases were seen relatively late, four days or later, in the course of the pneumonia. Of these, the degree of distention was as follows: Grade 1, 7 cases, Grade 2, 53 cases, Grade 3, 40 cases.

The length of time the rectal tube suction siphonage was used is shown in table 2.

TABLE II

	12 to 24 hrs	2 to 4 days	4 to 6 days	Longer than 6 days
Successfully deflated	69 cases	6 cases	3 cases	9 cases
Partially deflated—6 cases	<i>Total—87% successfully treated, 6% partially successfully treated, 7% complete failure</i>			
Unsuccessfully treated—7 cases				

Most of the cases were controlled within 24 hours, only 18 per cent of the successfully treated cases requiring a longer period for control. The partially deflated and unsuccessfully treated were treated over an indefinite period before being discontinued. It was in these 13 per cent that the rectal irritation occurred.

The rate of death and recovery of these cases is as follows:

TABLL III

	10 to 19 yrs old	20 to 29 yrs old	30 to 39 yrs old	40 to 49 yrs old	50 to 59 yrs old	60 to 69 yrs old	70 to 79 yrs old	80 to 89 yrs old
Lived	8	10	16	18	4	4	0	0
Died	1	8	8	6	8	6	1	2
Total	9	18	24	24	12	10	1	2
Total died				40%				
Total lived				60%				

It was noted that in 34 per cent of these cases the distention was completely controlled without influencing the fatal termination of the disease. In only two cases unsuccessfully treated did the distention seem to be a direct cause of death. However, we believe that the distention was a true indication of the degree of toxemia present, the severest distention invariably occurring in the most toxic patients.

In addition to the actual deflation the procedure has been of great value in other ways. Our patients have received more rest (the prime requisite in any régime of treatment for lobar pneumonia) than they did before the introduction of this treatment. The patient does not need a bed pan frequently, and there is no straining to add to the load of a weak heart. We have had patients so treated who have not needed a bed pan for 96 hours during which they were perfectly at rest. The procedure has been especially helpful in this respect in the case of patients treated in oxygen tents. The nursing problem is simplified by lesser need of moving the patient. Incontinence of feces occurred only twice in the 100 cases reviewed. Our experience with the practical application of this method of treatment makes us feel that it is very well adapted to use in the home as well as on the hospital wards.

CONCLUSIONS

1 Abdominal distention is the commonest complication in lobar pneumonia. When extreme it may be a contributory factor in the mortality rate.

2 Rectal suction siphonage is a safe, inexpensive, and effective method of relieving abdominal distention, and has been a great comfort to our patients.

The authors wish to express their appreciation to Miss Blanche Loeb Langsdorf for her valuable assistance in collecting statistics for this paper.

REFERENCES

- 1 SIBSON, F. Brit Med Jr, August 2, 1873
- 2 SCHOEN, McIVER, REDFIELD, and BENEDICT. Am Jr Surg, August, 1933
- 3 CUTTING, R. A. Principles of preoperative and postoperative treatment, Am Jr Surg, 1931, 21, 561

- 4 VON BUNGLE Lehrbuch der Physiologie des Menschen, 2d Ed, 1905, F C W Vogel, Leipzig
- 5 McIVER, M A, REDFIELD, A C, and BENEDICT, E B Gaseous exchange between blood and lumen of stomach and intestines, Am Jr Physiol, 1926, lxxvi, 92-111
- 6 SPENCER, H J Constipation, Am Jr Digest Dis and Nutr, 1935, ii, 7-13
- 7 ALVARFZ, W C The mechanics of the digestive tract, 2d Ed, 1929, Paul B Hoeber, Inc, N Y, p 34
- 8 WIGGERS, C J Physiology in health and disease, 1934, Lea and Febiger, Philadelphia
- 9 KANTOR, J L, and MARKS, J A Study of intestinal flatulence, ANN INT MED, 1929, iii, 403-422
- 10 OGLE, J W Lancet, July 9, 1887
- 11 HICKS, BRAXTON Trans Obst Soc, 1869
- 12 AILBUTT, CLIFFORD Practitioner, 1869
- 13 BROADBENT, W H Cases of paralysis of cranial nerves, Brit Med Jr, 1879, ii, 87-89 A case of intestinal obstruction successfully treated by puncture of the small intestine, ibid, ii, 490
- 14 ORR, T G Treatment of postoperative "gas" pains, Ann Surg, 1931, xciv, 157
- 15 HENJERES, A W Postoperative tympanites, New York State Med Jr, 1931, xxxi, 74
- 16 NOTHNAGEL Über die Einwirkung des Morphium auf den Darm, Arch f path Anat, 1882, lxxvix, 1-8
- 17 UHLMANN, F, and ABELIN, J Beiträge zum Opiumproblem, Ztschr f exper Therap, 1920, xxi, 58-96
- 18 KING, C E, and CHURCH, J G Motor reaction of muscularis mucosae to some drugs, Am Jr Physiol, 1923, lvi, 428-436
- 19 PIANT, O H, and MILLER, G H Effects of morphine and other opium alkaloids on muscular activity of alimentary canal, Jr Pharm and Exper Therap, 1926, xxvii, 361-383
- 20 OLIVER, G, and SCHAFER, E A On the physiological action of extracts of pituitary body and certain other glandular organs, Jr Physiol, 1895, viii, 276-279
- 21 WEILAND Zur Kenntnis der Entstehung der Darmbewegung, Arch f d gesamt Physiol, 1912, cxlvii, 171-196
- 22 GROSSMAN Über die klinische Brauchbarkeit des Cholins, München med Wchnschr, 1920 lxxii, 251
- 23 GUGGENHEIM and LOEFFLERS Über des Vorkommen und Schicksal des Cholins im Tierkörper, Biochem Ztschr, 1916, lxxiv, 208
- 24 DALE, H H Action of certain esters and ethers of choline, Jr Pharm and Exper Therap, 1914, vi, 147-190
- 25 WOLFE, C G L, and CANNEY, J R C Treatment of ileus by choline, Lancet, 1926, i, 707-709
- 26 LEHEUX, J W Cholin als Hormon der Darmbewegung, über den Einfluss des Cholins auf die normale Magen-Darmbewegung, Arch f d gesamt Physiol, 1921, cxc, 301-310
- 27 CARLSON A J, SMITH, E A, and GIBBENS, I Action of choline on alimentary canals of intact dogs, Am Jr Physiol, 1927, lxxxi, 431-435
- 28 OCHSNER, A, GAGE, I M and CUTTING, R A Value of drugs in relief of ileus, Arch Surg, 1930, xxi, 924-958
- 29 PAINE, J R, CARLSON, H A, and WANGENSTEEN, O H Postoperative control of distention, nausea and vomiting, Jr Am Med Assoc, 1933, c, 1910-1917
- 30 PAINE, J R, and PHILLIPS, E C Nasal catheter suction-siphonage, Am Jr Nursing 1933, xxxiii, 525-533

THE RÔLE OF ACCIDENTAL PUNCTURE OF VEINS IN THE PRODUCTION OF ALLERGIC SHOCK

By G L WALDBOTT, M D , F A C P , and M S ASCHER, M D ,
Detroit, Michigan

IN spite of many publications on the prevention of allergic shock following injections of pollen and serum, there remains a great deal of uncertainty concerning its causes and prevention. This is well illustrated by the fact that even those clinicians who are most experienced in the administration of hypodermic medication are still completely at loss to explain certain reactions. Piness,¹ for instance, stated, in 1934, that despite the most careful gauging of doses there are reactions for which we are unable to account.

The importance in this connection of accidental intravenous injection of the allergen is not sufficiently stressed. In a paper dealing with the prevention of reactions, Rudolph and Cohen² fail to emphasize the rôle of accidental puncture of veins in the production of reactions. Others (Duke,³ Insley⁴) have proposed valuable measures to prevent shock, but do not propose means practicable for the general practitioner to prevent accidental intravenous injections. Commercial houses marketing serum and pollen extracts have greatly neglected to stress this feature in their directions to physicians. Yet, with few exceptions, the accidental intravenous administration of serum or pollen accounts for the fatal outcome in most cases of sudden death reported in the literature following injections.⁵ It will be shown below that this constitutes a great menace in the giving of pollen injections.

Within the past few years we have been able to reduce the incidence of reactions from pollen injections to a marked degree by observing certain precautions outlined elsewhere.⁶ These measures take into consideration the fact that severity of a reaction depends upon the state of sensitivity,[†] the rapidity of absorption of the antigen, and the degree of the overdose. In addition to an actual overdose due to error, to incorrectly judging the patient's degree of sensitivity or to switching from an old to a new extract, the following factors may contribute to the effect of an overdose. Simultaneous absorption of the same or another antigen to which sensitivity exists, by either the intestinal route (food), the respiratory route (pollen), or from the site of previous injections, or simultaneous absorption of bacterial materials from an infection present in the system.

Regardless of these precautions which were directed toward prevention of an overdose, reactions occurred, and, as a rule, were decidedly more

* Received for publication June 29, 1935.

† Whether this sensitivity is inherited (atopic) or acquired ("anaphylactic") does not alter in the slightest degree the symptomatology of shock.

severe than those formerly encountered During the past hay-fever season we made observations concerning the relative frequency of accidental puncture of small venules, the diagnostic features connected with a reaction so produced, and the best methods of avoiding such mishaps

DIAGNOSTIC CONSIDERATIONS

A puncture of a vein may result in two clinically distinct types of reactions, depending upon whether the extract is injected directly into the blood stream ("intravenous" reaction) or seeps into a small punctured venule soon after the injection ("backseepage" reaction)

1 *Intravenous Reactions* The characteristic features of this type of reaction are the unusual severity of the manifestations and the absence of a local swelling at the site of injection In a reaction due to inaccurate dosage, no matter how large the overdose may have been, there is always a time interval of a few minutes during which a more or less marked wheal arises on the site of injection Often a reddened, more or less itchy, area can be noted along the lymph channels, similar to that seen in lymphangitis, before generalized urticaria and respiratory symptoms occur In an "intravenous" reaction proper, skin manifestations are usually of little moment throughout There is a decided prevalence of internal manifestations, particularly, of symptoms which can be attributed to edema of the lungs, and probably, of the liver This is well in accord with Kahn's⁷ recent observations that in shock produced in animals by the intravenous route there are considerably less skin-reacting antibodies present than if the shock-producing injection is made subcutaneously Another distinctive feature is the absence of allergic symptoms after the reaction is controlled While in "non-intravenous" reactions urticaria and other allergic symptoms may recur several hours after their control by epinephrine, an "intravenous" reaction produces its full effect immediately, little, if any, after-effect is noticeable with the exception of a generalized weakness or a low-grade pulmonary infection This latter condition has been explained as due to secondary infection of residual areas of pulmonary edema (Waldbott and Snell⁸) The following is an instance of an "intravenous" reaction

Case 1 J K, a 17 year old hay-fever patient, had been successfully treated in 1932, in one of the dispensaries with which we are connected He had the eighteenth injection of 1933, consisting of 10,000 units each of small and giant ragweed and cocklebur on July 7 On July 14, at 10 01 a m, he received 12,000 units of the same pollen extracts Within 20 seconds following the injection, he noticed a strange taste in his mouth, "tingling around the heart" and difficulty in breathing Ten seconds afterwards he collapsed and became pulseless A tourniquet was immediately applied by the attending nurse and 0.5 cc of epinephrine was given subcutaneously (10 03) The same amount was repeated at 10 05 by Dr S R After the second injection of epinephrine the pupils reacted slightly to light and consciousness was regained for about three minutes The pulse was not palpable at the time At 10 08, 10 cc of epinephrine was given intramuscularly The pulse became noticeably stronger and the respirations assumed a more regular character From 10 03 to

10 55 the tourniquet was loosened only three times for a period of a few moments, and entirely removed at 10 55 Outside of the usual effect of epinephrine and an unusual degree of general weakness which lasted for several days there were no noticeable allergic symptoms after the incident There was no urticaria, either localized or generalized Not the slightest local reaction was present at the site of injection Although no further treatment was given during the balance of the hay-fever season, the boy remained free from hay-fever

Comment One is particularly impressed first with the unusual severity of the clinical manifestations, resulting in this case in complete pulselessness, and second with the absence of urticaria and local swelling, and of any material after-effect We feel that in this case the life of the patient was saved by the immediate administration of large doses of epinephrine, and that the application of the tourniquet was of no avail

CHART I
Differential Features of Intravenous Reactions

	Overdose	"Backseepage"	"Intravenous"
Premonitory Evidence	Rapid appearance of local wheal	Bleeding at site of puncture or bloody suffusion	
Local Reaction	Speed of appearance and size of wheal indicates severity	Occasionally bloody suffusion under skin	None
Time Interval	Proportional to amount of overdose (5 minutes to 2 hours)	Between one to five minutes	10 to 30 seconds
<i>Symptoms</i> Urticaria	Marked	Extreme at onset	Little, if any
Respiratory	Hay-fever, bronchitis, asthma	Hay-fever, bronchitis, asthma	Pulmonary edema
Collapse	Negligible	Marked	Extreme
Others	Flare-up of previously existing allergic or non-allergic foci		Prostration, cyanosis
Duration	Prompt control by epinephrine Urticaria may recur	Symptom-free after control	Generalized malaise for several days
After-Effects	Relief of allergic symptoms unless the overdose too drastic		Broncho-pneumonia may ensue
Response to Treatment Epinephrine	Promptly to 1/10 to 3/10 c c , repeated if symptoms recur	Larger doses (0.5 to 1.0 c c) needed immediately	
Tourniquet	Useful In extreme cases incision of site of injection	Useful	Of no avail

2 "*Backseepage*" Reactions While to our knowledge only four truly "intravenous" reactions were encountered within the past three seasons in a series of 41,037 injections, there is another more common source of dangerous reactions, which has not been sufficiently emphasized i.e., the puncture of a vein and backseepage into the blood stream. This occurred 34 times in this series. In the hypodermic administration of pollen and serum, it is relatively common that a small venule or capillary is punctured. Should any of the injected material ooze into the punctured venule, the reaction resulting would be similar to that of a true "intravenous" reaction. This type of reaction can usually be recognized by the following evidence. Presence of blood on the site of injection or a bloody suffusion under the skin which becomes rapidly replaced by a wheal. Generalized allergic symptoms occur within one to five minutes and are unusually severe. They consist of both cutaneous and internal manifestations, in contradistinction to the true "intravenous" reaction where skin manifestations are either absent or slight. Dermal edema is intense and can often be seen to spread rapidly from the site of injection over the entire body surface. Collapse occurs within a few minutes if the reaction is severe or not immediately controlled. Since instituting the precautions mentioned below, the incidence of these reactions has been reduced but not entirely eliminated. Chart 2 is a tabulation of the incidence of the different types of reactions, chart 1 presents their differential diagnostic features.

CHART II
Incidence of Reactions Encountered During 1932-1934

Year	Number of Injections	Reactions Encountered					
		Total Number	Incidence	"Intravenous"	Incidence	"Back-seepage"	Incidence
1932	9898	36	1 276	1	1 9898	11	1 899
1933	12364	44	1 280	1	1 12364	14	1 883
Total 1932-1933	22262	80	1 278	2	1 11131	25	1 890
1934	18775	61	1 308	2*	1 9387	12	1 1564

* Only a small portion of the extract was injected since the accidental puncture of the vein was recognized during the injection (repeated retraction of plunger of syringe)

EVALUATION OF THE CUSTOMARY MEASURES OF CONTROL

The measures which have been advocated for the control of reactions from pollen extracts are the application of a tourniquet above the site of injection and the administration of epinephrine^{3,4}. Recently, Rice⁹ demonstrated that the absorption of epinephrine may be controlled similarly to

that of the pollen extract by applying a second tourniquet above the site of the injected epinephrine. In extreme cases incision of the site of injection after the application of a tourniquet above may be resorted to.

These measures, although they are entirely satisfactory for reactions due to overdose, in our experience have proved inadequate to prevent reactions due to puncture of veins. Duke³ considered the accidental puncture of venules when he advocated the administration of epinephrine and ephedrine simultaneously with a small portion of the pollen extract. Only after noting a preliminary subcutaneous blanching does he inject the remaining amount. There are two definite disadvantages to this procedure. First, these drugs delay or prevent the occurrence of a local swelling which serves as a gauge for subsequent injections and thus make further treatment more difficult. Second, there is the well-known effect of even small doses of epinephrine which has often discouraged patients from continuing further treatment.

CHART III
Comparison of Potential and Actual Reactions in 1934
(In 18,775 Injections)

	Number	Incidence
Blood in Syringe (Retraction of plunger)	12	1 1564
No Times Blood on Cotton	104	1 180
"Intravenous" Reactions	2	1 9387
"Backseepage" Reactions	12	1 1564

PREVENTION OF "INTRAVENOUS" AND "BACKSEEPAGE" REACTIONS

If for these reasons, one does not wish to avail himself of Duke's method, the following precautions are suggested for the prevention of reactions due to puncture of a vein.

1. Care in selecting an area for injection which is not highly vascularized. Such a suggestion may seem superfluous, had we not encountered patients in whom blood was noted on retracting the plunger on repeated occasions. In five cases this occurred more than twice in the same person and, in one individual, blood was recovered on four different occasions. After a more careful inspection of the skin we were able to discern small veins which had been punctured and which we had previously overlooked. We are now in the habit of inspecting the prospective area very carefully, paying attention to good lighting conditions, and having the patient open and close the fist after the venous return had been compressed manually.

* The value of the last mode of treatment is well illustrated by the following case. In a patient (E. P.) an extreme overdose of cotton extract had been given because of an incorrect estimation of the patient's degree of sensitivity. Within two minutes after the injection a markedly itching area had arisen and generalized symptoms seemed imminent. Upon incision of the wheal after a tourniquet had been applied above the site of injection, most of the extract mixed with blood was recovered and relatively little epinephrine was required to prevent disagreeable after-effects.

above the elbow. The injections are given in the subcutaneous regions of the extensor surface of the forearm, in order that sufficient space for the application of a tourniquet and the administration of epinephrine be available.

2 Repeated withdrawal of plunger. This precaution, we feel, constitutes a definite aid in the prevention and control of intravenous reactions. As shown in chart 3, there were 12 occasions in a series of 18,775 injections during the course of which blood appeared in the syringe. In two different instances blood was noted only after the second or third retraction of the plunger and after a small portion of the extract had been administered. This was apparently due to the fact that the needle was displaced after its first insertion into the skin. Although the needle was immediately withdrawn, the ensuing reactions were unusually severe. How small a fraction of a routine dose may thus account for rather alarming symptoms can be seen from the following instances.

Case 2 Mr. A. M., a pollen asthmatic undergoing perennial treatment, had reached 7200 units of both small and giant ragweed on July 26. On August 2, he was to receive 7500 units of the same pollen extracts. After a preliminary withdrawal of the plunger, after only about one-fifth of the contents of the syringe had been administered, a second withdrawal of the plunger disclosed blood in the syringe. The needle was immediately withdrawn. Almost immediately the patient noticed a marked burning sensation in the abdomen and about the mouth. He became extremely short of breath. In the meanwhile, he was given 10 c.c. of epinephrine and a tourniquet was applied above the site of injection. Marked cyanosis and collapse ensued. At that time a slight edema of the face was noted. A second injection of epinephrine, 10 c.c., was given subcutaneously. After three minutes he regained consciousness, his breathing became easier, and within a short time no symptoms were noticeable other than those attributable to the effect of epinephrine.

Case 3 Dr. E. J., a 52 year old pollen asthmatic, was to receive an injection of 10,000 units of small and giant ragweed on July 24. The needle was inserted and the plunger withdrawn without noticing any blood in the syringe. After only a few drops of the extract had been injected, a second withdrawal of the syringe disclosed blood in the syringe. The needle was immediately withdrawn, a tourniquet applied above the site of injection. Within 45 seconds the patient complained of a spastic contraction of his chest, followed by marked wheezing and dyspnea. Epinephrine (0.5 c.c.) had already been given by this time. No dermal manifestations or collapse occurred. The reaction gradually subsided.

At several occasions it was found that in spite of repeated retractions of the plunger, no blood was noted in the syringe even though a venule had evidently been punctured. The plunger used was obviously not sufficiently tight-fitted. We, therefore, replaced the syringes with asbestos-wrapped pistons by syringes with more tight-fitting glass plungers for the administration of pollen extracts. We feel that this has contributed to the reduction of the incidence of this type of reaction.

3 Watching the area of injection for blood. Another means of recognizing a punctured vein is the appearance of blood at the site of injection. While the presence of blood does not always indicate an imminent reaction, a precautionary small dose of epinephrine (0.2 c.c.) and the application of

a tourniquet will largely obviate the danger of a "backseepage" reaction, considering the fact that there is always a time interval of from one to five minutes before "backseepage" reactions occur

4 Tight pressure upon the injected area It is impossible to furnish data to prove the effectiveness of this procedure, but it is felt that it tends to prevent the occurrence of "backseepage" reactions by occluding through pressure small venules which might have been punctured

5 Epinephrine It may seem that the measures suggested here are concerned with the prophylaxis of reactions due to punctured veins rather than with their treatment Since the outcome of the treatment depends entirely upon the rapidity with which epinephrine can be administered, the early recognition of this type of reaction is of the utmost importance

Every patient should be instructed about the symptoms of "intravenous" reactions If there is the slightest suspicion of the puncture of a vein, 0.2 to 0.3 cc of epinephrine should be given immediately If the symptoms of an impending reaction should then ensue, the first injection of epinephrine should immediately be followed by a larger amount (0.5 to 1.0 cc) of epinephrine

While these observations were made on patients receiving pollen extracts, they are applicable to injections of serum or of any other antigen to which unusual sensitivity exists

DISCUSSION

It may seem unusual that small amounts of intravenously-administered pollen extract are of such significance in the production of severe reactions inasmuch as Lichtenstein¹⁰ has shown that pollen treatment can be given by the intravenous route In his procedure, however, he was required to give initial doses, which were much smaller than is customary in ordinary treatment, and thus he probably built up a specific protection for this type of treatment If, as Kahn's⁷ work suggests, in intravenous therapy a different type of antibody is prevalent, one may assume that hyposensitization treatment by the subcutaneous route does not produce the protection required for intravenous treatment, and vice versa

Concerning the medico-legal aspect of this problem, the liability to which physicians are susceptible in pollen therapy should be pointed out, if they have not available for immediate use a fresh solution of epinephrine Some physicians have their nurses administer the injections of pollen and serums Others make it a practice to allow their patients to administer the injections themselves, especially those who have been in the habit of giving themselves epinephrine An emphatic warning must be given against such practice The neglect to observe the patient for at least five to ten minutes after the injection is another matter, which, in our opinion, may involve legal entanglements As pointed out, the reactions due to "intravenous" administration occur within a relatively short interval, and, moreover, the beginning of a reaction due to an overdose will become noticeable within that period of time, by the appearance of an unusually marked local edema

SUMMARY

1 In the treatment with pollen extracts, the accidental puncture of veins and administration of the extract into the blood stream constitutes a grave emergency

2 In 41 037 injections 38 such reactions were encountered, 4 of which were due to direct introduction of the extract into the blood stream ("intravenous" reactions) The remaining were "backseepage" reactions due to subsequent flow of the extract into a previously punctured venule

3 A clinical differentiation of true "intravenous" and "backseepage" reactions from those due to an overdose is outlined

4 Only a small fraction of the routine dose, if accidentally introduced into the blood stream, is necessary to cause unusually severe symptoms

5 The measures usually advocated for the prevention and treatment of reactions are discussed as adapted to reactions due to punctured veins The following additional suggestions for their early recognition and control are presented Care in avoidance of visible veins in the selection of the site of injection repeated withdrawal of the plunger before and during the injection for evidence of blood, watching the site of injection for subsequent bleeding and subcutaneous hemorrhage, and pressure upon the site of injection

6 The rapidity with which epinephrine is given determines the course of the "intravenous" and "backseepage" reactions The application of a tourniquet is an aid in controlling a "backseepage" reaction, but is of no avail if the pollen extract has been injected directly into the vein

7 In contrast to an incidence of one "backseepage" reaction in 890 injections, only one such reaction in 1564 injections was noted in 1934 since instituting the above precautions In the two instances of "intravenous" reactions, only a small portion of the routine dose was administered due to early recognition

BIBLIOGRAPHY

- 1 PINESS, S Discussion, Jr Allergy, 1934 vi, 99
- 2 RUDOLPH, J A, and COHEN, M B Types of human hypersensitiveness, their relationship to liability to serum reactions, Jr Am Med Assoc, 1934, cii, 900
- 3 DUKE, W W New method of administering pollen extract for purposes of preventing reactions, Jr Am Med Assoc, 1930, xciv, 767
- 4 INSLEY, S W The control of immediate shock following hypodermic medication, Jr Am Med Assoc, 1930, xciv, 765
- 5 WALDBOTT, G L The prevention of anaphylactic shock, Jr Am Med Assoc, 1932, xcvi, 446
- 6 WALDBOTT, G L Systemic reactions from pollen injections, Jr Am Med Assoc, 1931, xcvi, 1848
- 7 KAHN, R L Study on tissue reactions in immunity, comparative response following intravenous and intradermal injections of organisms, Jr Immunol, 1933, xxi, 339
- 8 WALDBOTT, G L, and SNELL, A D Pulmonary lesions resembling pneumonia as the result of allergic shock, Jr Pediat, 1935, vi, 229
- 9 RICE, R M Method of controlling pollen reactions, Jr Am Med Assoc, 1934, cii, 1222
- 10 LICHTENSTEIN, M R Intravenous pollen therapy, Jr Allergy, 1934, v, 231

SCHILLER, THE GREATEST OF THE MEDICAL POETS

By LOUIS H. RODDIS, F A C P, Commander, Medical Corps, U S Navy

JOHAN CHRISTOPH FRIEDRICH SCHILLER, the poet and friend of Goethe, was born November 10, 1759. November 10 was the birthday of another medical poet, Oliver Goldsmith, born 31 years before in 1728.

Schiller's place of birth was the little town of Maibach in Württemberg, Germany, situated in a district of the Rhine valley long famous for the beauty of its scenery and the richness of its agriculture. The eminent German soldier Von Hutten, known to medical men principally for his connection with the early history of syphilis, who spoke with authority for he had travelled in all parts of the Fatherland, said of Württemberg in a letter written in May 1517, "There is scarcely a more beautiful neighborhood in all Germany than the Province of Württemberg. The soil is excellent, the climate mild and wholesome, mountains, valleys, meadows, streams and forests interspersed in pleasing variety. The products of the earth are unusually abundant, the wine is like the country. The Swabians call Stuttgart the Earthly Paradise, so charming is the situation of the town." This encomium is well deserved. The pine clad slopes of the Black Forest bound it on the south, while vineyards, fields, villages, cities, cathedrals, and ruined castles along the Rhine and the Neckar add to the scenic beauty of the district and make it an idyllic homeland for a poet. Schiller's attachment to his home was deep and romantic, and this feeling exercised a powerful influence over his life and poetry.

The father of the poet had himself been apprenticed to a surgeon, and served in that capacity in the Bavarian Army throughout the campaigns in the Netherlands during the Wars of the Spanish Succession. Later he was commissioned as Ensign and Adjutant by the reigning Duke of Württemberg who, after the Peace of Paris, continued him in his service, advanced him to the rank of Captain and Major, and employed him as his chief forester. This was a task to which he was peculiarly suited as he had a great interest in forestry and landscape gardening. The remainder of his life was spent in the establishment of nurseries, the planting of trees and the improvement of the grounds at the Duke's beautiful forest castle "Die Solitude" or "The Solitude." He is said to have planted and raised from seeds 60,000 forest trees. He published a book on forestry, and lived to enjoy the fame of his son. He was evidently a man of forceful character, practical, conscientious

* Received for publication December 2, 1935

This is the seventh of a series of portraits of medical poets. Those which have previously appeared in the *ANNALS OF INTERNAL MEDICINE* are Joseph Rodman Drake, February, 1929, Oliver Wendell Holmes, June, 1930, Oliver Goldsmith, May, 1932, Wm. Savage Pitts, January, 1933, Lieutenant Colonel John McCrae, June, 1933, Dr. Richard Shuckburgh, June, 1934.

and deeply religious. The mother had a less strongly marked personality though she was affectionate and devoted. While it has been the fashion to state that the remarkable qualities of so many great men were received from their mothers, it seems more than likely that in the case of Schiller much of his strength and ability were derived from his sire.

Fritz, as most German boys named Friedrich are called, received his first school instruction from Philip Moser, the Lutheran pastor at Lorch, for though born in southern Germany where Catholicism was the prevailing religion, Schiller's people were Protestants. It was the desire of the parents that their boy should enter the church, and indeed he seems to have had an inclination for it. We have a charming account, by one of his biographers, of Schiller as a boy of five or six years playing at being a pastor. He would tie one of his mother's black aprons about his neck in the manner of a surplice, put on a cap, and standing on a chair as a pulpit he would deliver a sermon, very serious about it all and much offended if anyone laughed at him.

The reigning prince of Württemberg was a petty tyrant, full of energy and bustle, who, after a life of extravagance and dissipation, proposed to devote the later years of his life to good works. One of his hobbies was a military academy at Stuttgart, and here was placed young Schiller to be educated at the expense of the prince. The boy, however, had no choice as to the course he should like but was compelled to study law though his parents desired him to study theology. He finally obtained permission to give up the law but only on the condition that he would study medicine. His entrance into our profession was, therefore, due to chance and necessity rather than to any interest in the subject.

The life of the students at the Academy was more like that of prisoners than scholars, and the strictest military formalities were observed. "It was a strange sight," says Nicolai (*Travels Through Germany*) who visited the Academy, "when at the dinner hour the pupils, in two columns, the nobles to the right and the burghers to the left, filed solemnly into the dining hall without the slightest betrayal of pleasure so natural to boys at the sight of food. 'Front,' 'to the right,' 'to the left,' were called out as they reached the tables. When the command was given with a loud clap to say grace, all hands were folded, and, the prayer ended, each unfolded his hands, took hold of the chair to perfect time, pulled it out and sat down, just as a battalion of soldiers fire at command. Indeed, I am almost sure they kept time as they put their spoons into the soup."

It was in such an atmosphere that Schiller pursued his medical studies. His favorite reading was Luther's translation of the Bible, and Plutarch, and the German poets Lessing, Goethe, and Klopstock. The birthdays of the reigning prince and of prominent members of the court were celebrated by plays and musical festivals. Schiller wrote his first published poem for one of these occasions, printed in the *Suabian Magazine*, a local monthly periodical. In 1779 he produced a thesis "The Philosophy of Physiology," first



FIG 1 JOHAN CHRISTOPH FRIEDRICH SCHILLER

written in German and then translated into Latin. This essay did not receive the approbation of the authorities and Schiller was compelled to spend an additional year in study. The following is the Prince's comment to the Principal of the Academy: "I must confess there are some fine points in

pupil Schiller's essay and plenty of enthusiasm. But I do not wish it to be published and think it will be better for him to remain in the Academy another year until his enthusiasm has cooled off somewhat and then, if he continues to be industrious, he may become a great man." For once condescending mediocrity was right. Pupil Schiller did become a great man. The august and pedantic old prince did not realize that he really was a prophet.

The next year Schiller was more successful with his essay "The Connection of the Animal Nature of Man with the Spiritual." This was published as was a Latin dissertation required of him on inflammatory and putrid fevers.

He was now considered to have completed his professional training and was appointed Surgeon to the Regiment of Grenadiers, then in garrison at Stuttgart. As a free pupil at the Academy he was bound to the service of the reigning ducal house of Wurtemberg. Thus at 21 he found himself a military surgeon with a salary scarcely sufficient to support himself. He lodged with a former comrade at the Academy, Lieutenant Kapf, in a house in the Eberhards Strasse kept by a blond widow of 30, Frau Wischer or the "Vischerin." Kapf and Schiller shared a little room here which they referred to as "The Kennel." Here they occasionally entertained their bachelor friends with smoked sausage, potato salad and beer with plenty of tobacco smoke for a background. They had a soldier servant, Private Kronenbitter, with a uniform "adorned with patches." The poet Scharffenstein, who was a frequent visitor, describes Dr. Schiller as rigged in "a uniform of the old Prussian cut, rolls (which were intended for curls) on each side of his face, the military hat which was hardly large enough to cover his head and from under which hung his long thick queue. Around his neck he wore a stiff stock of horsehair."

During the later years at the Academy and the first months as an Army surgeon Schiller wrote his first great work, the tragedy called "The Robbers." The appearance of that poem and its almost immediate success on the stage soon made the 21 year old Army doctor famous throughout Germany. Scherr tells of his stealing away at this time from his duties without leave, accompanied by a comrade journeying to Mannheim to see a performance of his play, and "very near being too late, detained by the charms of a pretty barmaid on the way." "Happy carelessness of youth," says this biographer, "which, even on the threshold of a great event, could be stayed by the bright eyes of a barmaid."

The tyrannical old Prince of Wurtemberg did not approve of his Army surgeons becoming poets. He felt it was a waste of state education, and some of the liberal sentiments expressed in "The Robbers" were also not to his liking. Schiller was forbidden to publish any more poetry without first passing it through the hands of the censor. This and the fear of imprisonment led to Schiller's decision to flee from the service of the Prince and to devote himself entirely to literature. It was a decision which of

couse separated him from any hope of official position in Wurtemberg and also separated him from medical practice, though to the end of his life he maintained considerable interest in medicine and on a number of occa-



FIG. 2 The statue of Schiller in Como Park, St. Paul, Minnesota

sions when in isolated situations in the country he rendered professional services to persons in need of them

Schiller's next great literary work was the drama of "Don Carlos" which further increased his fame and led to the beginning of his friendship with Goethe and Humboldt. He began also his historical studies and in 1789 he was called to Jena to become the Professor of History at that cele-

brated university. The next few years saw his reputation as a historian established by his "History of the Revolt of the Netherlands," the "History of the Thirty Years War," and his historical essays. He also became deeply interested in philosophy and aesthetics, and his essays in these fields such as that on "Grace and Dignity," and "The Aesthetic Education of Man" still further enhanced his fame. It is unfortunate that a long cherished project for a German biographical collection modeled on Plutarch was never begun.

In February 1790 Schiller married the younger of two sisters, Charlotte, or as she was generally called, Lotte Leugenfeld. Schiller's pet name for her was "Lolo." The older sister Caroline also loved him but later married her cousin William von Wolzogen. His marriage was an extremely happy one, as nearly ideal apparently as it was possible to be. In 1797 he purchased a comfortable home near Jena surrounded by a pleasant garden and with an admirable view. He wrote in the spring of that year to Goethe "I salute you from my garden to which I removed today. A lovely landscape surrounds me, the sun is smiling with a friendly adieu and the nightingale is trilling. Everything around is cheerful and my first evening in my own house is of the happiest augury." This house stood on a gentle eminence at the end of a hedge-lined path called "Monks' Alley." Behind it on a slope of the hill was the garden full of flowers and vegetables planted together as was the custom in old-fashioned gardens. At the top of the slope was a clump of trees beyond which the ground fell away precipitously to the bed of the Leutrabach whose rushing waters could be heard below. At the top of the slope under a linden, a fir, and an acacia stood a little one room cottage which served as the poet's study. It is now torn down and a stone marked with the inscription "Here Schiller wrote his *Wallenstein*" indicates its former location. Beside it in an arbor was an old stone table where Schiller often sat when writing and where he often talked with Goethe. Here too he wrote many of his most famous lyrics including the "Song of the Bell," "The Glove," "The Hymn of Joy," "The Ring of Polycrates," and "The Dignity of Man." The dramas that followed, "Maria Stuart," the "Maid of Orleans," "William Tell," "Wallenstein," and the "Bride of Messina" placed Schiller among the greatest of the dramatic poets.

Though he had many love affairs before marriage Schiller was one of the most domestic types of men and was happiest in the enjoyment of his home and family life with his wife and four children. His literary success also gave him great pleasure. Both of his parents lived to see him recognized as one of the greatest poets of all time. But despite the happiness and satisfaction from these things his last days were clouded by ill health and financial worries. The latter were partly alleviated by a pension from the Duke of Weimar but work and pleasure were marred by frequent attacks of illness. The first of these attacks began in Jena in 1790 and was apparently a cholecystitis and hepatitis. Later attacks became more fre-

quent and severe and in the spring of 1805 a broncho-pneumonia as a complication ended his life. This was the year of Wagram and Trafalgar. He was but 45 years of age. As he was dying he replied to a question as to how he felt, "calmer and calmer." His widow and two sons and two daughters survived him. The news of his death, in the words of Carlyle, "Fell cold on many a heart, not in Germany alone but over Europe it was regarded as a public loss by all who understood its meaning." This well expresses the affection felt toward him by all ranks of society as a lover of human kind and a spokesman of the best and noblest feelings of humanity. He was beloved for these qualities as well as respected and admired for his genius. Modesty, uprightness, manliness, and love of liberty, and affection and devotion to friends and family were outstanding characteristics.

Physically he was tall and slender, blond, with abundant red hair. His countenance and head were fine and his expression and smile attractive and amiable. He usually held himself with almost soldierly erectness, a heritage in part of his earlier military training. In later years when walking by himself he often went with his eyes cast upon the ground so that he would often nearly pass acquaintances without speaking but when he heard their salutation "he would catch hastily at his hat and give his cordial 'Guten Tag'."

Schiller's intellect was remarkable for power, clearness and comprehensiveness. The nobility of his nature is seen throughout his works which shine with his love of God, country, liberty, home, men, women, children, nature, and life. A patriot in the best sense of that abused word he was able in "William Tell" to interpret nationalism in Switzerland and Germany, and in the "Maid of Orleans" the national aspirations of France.

His relatively short life had been full of accomplishment. A quotation again from Carlyle furnishes the most suitable conclusion to this sketch of the greatest of the medical poets, of whom medical men and particularly military medical men should be especially proud.

"The kingdoms which Schiller conquered were not won from one nation at the expense of suffering to another, they were soiled by no patriot's blood, no widow's, no orphan's tear. They were kingdoms conquered from the barren realms of Darkness, to increase the happiness and dignity and power of all men, new forms of Truth, new maxims of Wisdom, new images and scenes of Beauty won from the 'void and formless Infinite,' a possession forever to all the generations of the Earth."

Bibliographical Note Scherr, *Life and Times of Schiller*, written about 1860, can scarcely be spoken of too enthusiastically. It is a classic of biography, worthy to stand beside Lockhart's *Scott* or Boswell's *Johnson*. Other works of importance are Pallaske (2 volumes), Carlyle (a short but striking character study and appraisal of Schiller's genius), and the highly interesting biography by his sister-in-law, Caroline von Wolzogen.

The picture of Schiller reproduced here forms the frontispiece of Scherr's biography. The statue, a very handsome one, stands in Como Park, St. Paul, Minnesota, and is from a photograph taken by the writer.

CASE REPORTS

FELTY'S SYNDROME, REPORT OF A CASE WITH NECROPSY FINDINGS *

By ROBERT H WILLIAMS, M D, *Nashville, Tennessee*

In 1924, Feltv¹ reported five cases in which the chief disturbances were chronic arthritis, splenomegaly and marked leukopenia

In 1932, Hanrahan and Miller² reported a case with characteristics closely resembling those of Felty's cases, for which a splenectomy was performed with benefit both objectively and subjectively

In March 1934, Craven³ added another case, likewise treated by splenectomy with improvement Also in March 1934, Alessandrini⁴ reported a similar case in which splenectomy was advised, but refused by the patient

In April 1934, Price and Schoenfeld⁵ reported a case with complete post-mortem findings

Until the present, only nine cases with this unusual and interesting syndrome have been reported, and the case to be presented in this paper is, as far as can be determined, the second autopsy report of such a case

F R, a white male, married, chaplain, aged 54 years, was admitted to the Second Medical Service, December 1, 1933, with the complaint of migratory joint pain of 10 days' duration

Family history was irrelevant He was born in Ontario, lived in Boston for the past 37 years and was never in the tropics No history was obtained of malaria, typhoid, scarlet fever, tonsillitis, chorea or rheumatism before the present illness He had had no serious illnesses and had always been in good health Sore throats, colds and dental troubles have been rare No symptoms had been present referable to the cardio-respiratory, gastrointestinal or neuro-muscular systems For the past three years there had been nocturia, twice per night

The present illness had begun with chilliness, feverishness and languor two months before admission These symptoms had persisted, and 10 days before admission, following exposure to a cool breeze for 12 hours, there was an aching and swelling in the left hand, disappearing spontaneously after 16 hours Two days later there were pain and swelling in the right ankle, which cleared up considerably after 12 hours Three days later the left hand became quite weak but not very painful The day before admission, the feet began to swell and were very painful This was soon followed by pain and swelling of the left shoulder and right knee, the pain disappearing in 12 hours On the morning of admission there developed severe pain on motion in the right elbow

On examination, the patient was found to be well developed and nourished, with a richly tanned skin The eyes, nose, mouth, throat and chest showed nothing remarkable In the infraclavicular regions, there was slight dullness, bronchovesicular

* Received for publication September 6 1935

From the Mallory Institute of Pathology, Boston City Hospital

breath sounds and a few crackles following cough. There was also slight dullness over the apices, posteriorly. The firm, smooth, sharp edge of the spleen was felt two cm below the left costal margin. The liver was not felt. There was free motion of all joints, except the right elbow, with relatively little discomfort. Very slight distress was experienced in both ankle joints. The left hand and wrist were definitely swollen and showed slight pitting edema. There was slight pitting edema of the right hand. The right elbow was held in a slightly flexed position, and the patient could not achieve complete extension without suffering severe pain. There were no objective signs about this joint except limitation of motion. The right knee showed nothing remarkable. There was a small amount of fluid in the left knee, and the patella floated. Both feet from the ankles down showed slight increase in heat and definite pitting edema.

The patient stayed in the hospital for about seven weeks during which time the spleen remained palpable two cm below the costal margins. The total white count ranged around 3000. Roentgenograms on admission showed cloudiness of the outlines of the right elbow joint and hypertrophic arthritis of both knees with effusion. Roentgen-ray of the sinuses showed clouding of the right antrum. Prostatic smear revealed no gonococci. Two electrocardiograms, a roentgen-ray of the chest, two aerobic and anaerobic blood cultures, two agglutination tests for *B. melitensis*, two stool cultures, several urine examinations and a Wassermann test were all negative.

BLOOD STUDIES

	WBC in thous- ands	Pml s	Eosino- philes	Myelo- cytes	Meta- myelo- cytes	Young pml s	Lympho- cytes	Mono- cytes	RBC in mil- lions	Hgb	Reticu- locytes
12/ 2/32	3.2									83	
12/ 3/32	2.4		3				48				
12/ 5/32	2.2	48	1				51				
12/ 7/32	2.5	48	2				49				
12/18/32	2.3	44	2				54				
2/21/33	3.3	55		4	6	6	28	1	2.7	62	
2/23/33	2.1	45	1	2	5		43	1			
2/27/33	2.2	59	2		1	4	34		3.01	63	1
5/17/33	3.2	6	3	2	2	40	46	1	4.6	77	
6/20/33	4.9	3			2	35	58	2	4.3	90	
7/27/33	3.3	6				32	62		6.2	90	
12/21/33	4.8	49	2				34	0	4.3		0.5
5/23/34	3.6	32					65	3	4.8		
8/20/34	2.4	57	2	3	3	16	19		3.3		
8/21/34	2.2	40		3	4	21	29	1			2
8/22/34	1.6	9		9	1	47	20				
8/26/34	3.2	34		3	2	24	36				
8/27/34	2.9	12		2	3	49	28	1			

On tapping the left knee, December 9, 50 c.c. of yellow turbid fluid were obtained, the total proteins of which were 4.5, the non-protein nitrogen 29, sugar 124, polymorphonuclear leukocytes 60 per cent, eosinophiles 2 per cent, lymphocytes 2 per cent and monocytes 2 per cent. No organisms were found by smear or culture.

The patient's treatment consisted chiefly of salicylates orally, physiotherapy and free fluids. By December 17, he had obtained free motion in the right elbow and shoulder. By December 29, there were no joint symptoms except stiffness in the right shoulder and right elbow. During the last week, he was given mild exercise for the various joints. Preparations were made for him to convalesce in Florida.

During his stay in the hospital there was an elevation of the temperature from 99 to 100°, almost every evening, but never above 100.5°. The pulse likewise was elevated from 85 to 100.

peared with the beginning of the improvement in April and has not recurred. The tongue appears to be normal. Nor has there been any return of tetany. By June 4 the blood calcium was 10.5 mg per 100 cc. The appetite remained a ravenous one until about the middle of August since which time it has been normal. Bowel movements for months have been normal with one movement daily. The stools are not bulky and microscopically there is no excess fat. The abdomen is not distended nor has there been any gaseous indigestion the past several weeks. The patient enjoys a normally active life. There is still a small amount of edema of the ankles which disappears overnight. On June 3 the serum albumin was 3.9 per cent and the serum globulin 2.1 per cent. At that time being up and around a very little resulted in a rather marked leg edema. On September 25 the serum albumin was raised to 5.1 per cent and the serum globulin was 1.3 per cent. It was felt that the inanition edema was increased by a weakness of the heart muscle from starvation in spite of the rise of the blood pressure to 122 mm mercury systolic and 74 diastolic, a rise which has persisted up to the last examination.

The response of the blood was at first satisfactory although it was not remarkable in view of the considerable amount of parenteral liver given. The reticulocytes rose only to 4 per cent. After the initial rise to 59 per cent hemoglobin with a 2,790,000 erythrocyte count on the twelfth day there was difficulty in improving the blood picture. On the twenty-ninth day the hemoglobin had dropped to 47 per cent with 2,710,000 red blood cells. By that time the patient could tolerate iron without added abdominal distress so one gram of ferrum reductum was added daily to the other therapy. This resulted by September 25 in a hemoglobin of 84 per cent (Dare) with 4,590,000 erythrocytes, a color index of 0.9, the white blood cells numbering 6,450 with 58 per cent neutrophils, 39 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophiles.

Characteristic roentgen-ray pathology was not disclosed in the gastrointestinal examination conducted after recovery from the severe symptoms had taken place.

DISCUSSION

Although sprue is uncommon in Cuba¹⁶ this case must be considered as one of the tropical variety in spite of the fact that no *Monilia* could be found in the stools.

While there may have been a dietary deficiency before 1932 there certainly was a dietary deficiency after the teeth were removed. The sore mouth of the alveolectomy shortly became the sore mouth of sprue. There ensued a functional as well as perhaps an anatomical interference with the absorption of fats and other food elements. Anorexia, weakness, emaciation, flatulent indigestion, and fatty, bulky diarrhea resulted. Inanition caused a severe edema, a marked drop in blood pressure and a cardiac weakness. The hypocalcemia is explained on the basis of faulty absorption and reabsorption of calcium in the bowel because of formation of calcium soaps with the excess fat in the intestine as well as by poor absorptive power of the small bowel due to edema, atony, and from possible inflammatory changes.

Faulty absorption as well as inadequate ingestion of iron is an important consideration. It has been found that it is often necessary to give large doses of iron in order to obtain satisfactory blood response.⁹

For many years bizarre diets, all more or less rich in the extrinsic factor, have been moderately successful in the treatment of sprue.¹ Reduction

of fats in the diet has always been stressed and was followed in the beginning in this case. Snell⁸ emphasizes the use of vitamin D and calcium.

Since the introduction of the liver diet in the treatment of these cases by Bloomfield and Wyckoff¹⁷ in 1927, liver therapy has been found to be most satisfactory, probably because it contains more of the extrinsic factor as well as the hematopoietic substance. However, it was found that faulty absorption occasionally prevented adequate utilization of the liver, and parenteral liver extract was then used. According to the experience of Rhoads and Miller¹ much more liver extract was necessary to control the sprue symptoms than is commonly necessary in pernicious anemia. Their report detailed four cases which had been treated previously with rather large doses of parenteral liver extract and which did not respond until daily doses such as were given in this case were administered.

CONCLUSION

A case of sprue is reported illustrating the effectiveness of liver therapy.

BIBLIOGRAPHY

- 1 RHOADS, C P, and MILLER, D K. Intensive liver extract therapy of sprue, *Jr Am Med Assoc*, 1934, ciii, 387-391.
- 2 MACKIE, T T. Nontropical sprue, *Med Clin N Am*, 1933, xvii, 165-185.
- 3 SNELL, A M, CAMP, J D, and WATKINS, C H. Nontropical sprue, *Proc Staff Meet Mayo Clinic*, 1935, x, 177-185.
- 4 SNELL, A M, and CAMP, J D. Chronic idiopathic steatorrhea, *Arch Int Med*, 1934, liii, 615-630.
- 5 COMFORT, M W. The diagnostic value of steatorrhea and azotorrhea in chronic pancreatitis, *Med Clin N Am*, 1934, xviii, 519-529.
- 6 STURGIS, C C, ISAACS, R, GOLDHAMER, M S, BETHILL, F H, and FARRAR, G E. Blood, *Arch Int Med*, 1935, lv, 1001-1081.
- 7 SPIES, T D. The medical treatment of early pellagra, *Jr Am Med Assoc*, 1935, cv, 1028.
- 8 ASHFORD, B K. Sprue (*in* CECIL's Textbook of medicine, 1933, 390-394, W B Saunders Company, Philadelphia).
- 9 CASTLE, W B, and RHOADS, C P. The etiology and treatment of sprue in Puerto Rico, *Lancet*, 1932, i, 1198.
- 10 FAIRLEY, N H. Sprue, its applied pathology, biochemistry, and treatment, *Trans Roy Soc Trop Med and Hyg*, 1930, xxiv, 2.
- 11 LOW, G C, and FAIRLEY, N H. Fatal perforation of the cecum in a case of sprue, *Brit Med Jr*, 1934, ii, 678-679.
- 12 FAIRLEY, N H, and KELNER, T P. Gastro-jejuno-colic fistula with megalocytic anemia simulating sprue, *Brit Med Jr*, 1931, ii, 1335-1341.
- 13 CORR, P, and BOECK, W C. Chronic ulcerative enteritis, *Am Jr Dig Dis and Nutr*, 1934, i, 161-164.
- 14 RHOADS, C P, and CASTLE, W B. The pathology of the bone marrow in sprue anemia, *Am Jr Path*, 1933, 813-827.
- 15 MANSON-BAHR, P. On nontropical or indigenous sprue, *Jr Trop Med and Hyg*, 1929, xxxii, 118, 119.
- 16 AGRAMONTE, A. *Trans Internat Conference on health problems in tropical America*, Kingston, Jamaica, 1924, p 703, United Fruit Co, Boston.
- 17 BLOOMFIELD, A L, and WYCKOFF, H A. Remission in sprue following a high liver diet, *Calif and West Med*, 1927, xxvii, 659-660.

LOCALIZATION OF THE SITE OF EXPERIMENTAL PREMATURE CONTRACTIONS AND BUNDLE BRANCH LESIONS BY MEANS OF MUL- TIPLANE CHEST LEADS*

By JOSEPH WEINSTEIN, M D , and DAVID I ABRAMSON, M D ,
Brooklyn, New York

IN A recent publication,¹ the authors presented the results obtained in detecting and localizing experimental myocardial lesions by means of certain chest leads,² which differed in a number of respects from the others thus far employed. These experimental leads (designated as multiplane chest leads) consisted of combinations of linear electrodes placed on the anterior and posterior surfaces of the chest parallel to and beyond the estimated borders of the heart, in contra-distinction to the conventional chest leads, advocated by other investigators^{3,4,5} in which at least one electrode of sufficiently large circumference was placed on the anterior or posterior chest wall directly over the heart itself. In our experimental leads a number of recording planes were employed, these appearing to be responsive to electrical changes of even small magnitude. It was found that superficial cauterization of various parts of the epicardial surface of both ventricles consistently produced RS-T changes in the experimental chest lead tracings, whereas in only one-half of these cases were similar alterations noted with the standard three leads, and in two-thirds with Lead IV. At the same time it was found that the experimental chest leads generally indicated the ventricle involved.

The present work was undertaken in order to investigate in more detail the question of the value of these leads in localization. It is the purpose of this communication to report the electrocardiographic alterations observed in the experimental chest lead tracings following first, the artificial production of premature contractions from various parts of the ventricles, and second, the transection of either one or the other branches of the Bundle of His.

METHOD

The experiments were performed on cats under "Dial" anesthesia (intraperitoneal). The German silver electrodes used in our previous experiments were replaced by ones of steel wire (1/32 inch in diameter), since polarization was less often present with the latter. The sites of insertion of the electrodes, as well as the manner in which the animal was prepared

* Received for publication May 30, 1935

From the Department of Physiology and Pharmacology, Long Island College of Medicine, and from the Medical Service and Cardio-Vascular Laboratory of the Jewish Hospital of Brooklyn

With the technical assistance of Pearl Kramer

and the heart exposed, were similar in all respects to those used in the previous work¹

The following leads were employed (figure 1)

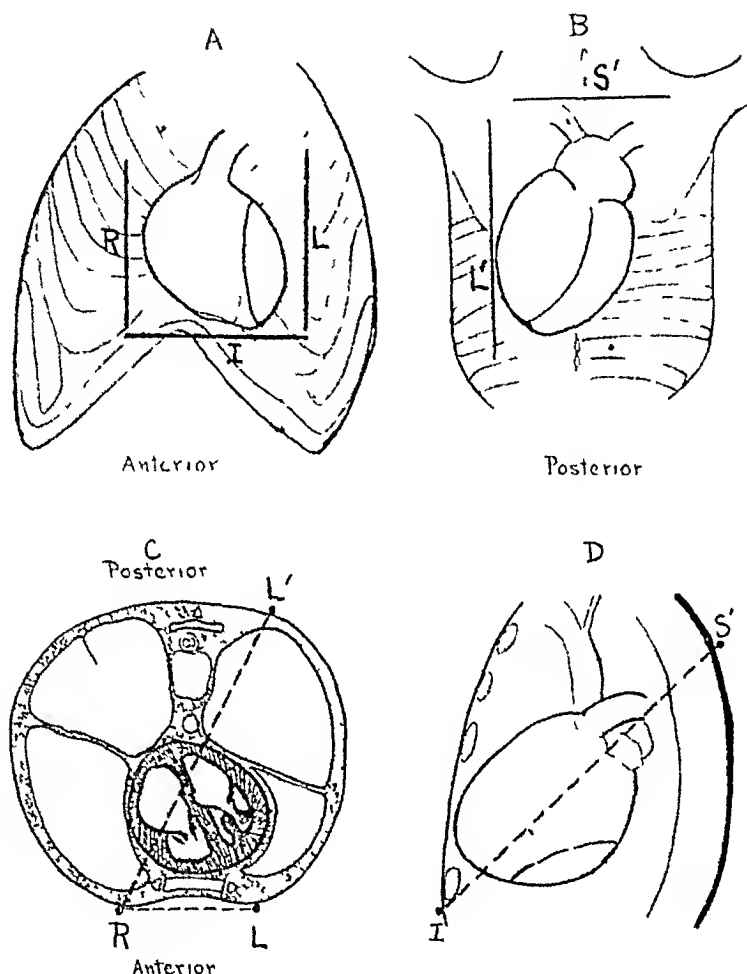


FIG 1, *A* and *B* Diagrammatic representation of the position of the experimental chest electrodes *A*, Anterior surface *R*, right electrode located some distance to the right of the sternum *L*, left electrode, extending in the left anterior axillary line parallel to electrode *R* *I*, inferior electrode, inserted somewhat above the level of the ensiform cartilage and extending across the chest *B* Posterior surface *S'*, superior posterior electrode, extending across the back at about the level of the superior border of the scapulae *L'*, left posterior electrode placed so as to correspond in position to *L* (left anterior electrode) *C* and *D* Cross section and lateral view of chest illustrating the various electrode combinations *L'R*, left posterior and right anterior electrodes *RL*, right anterior and left anterior electrodes *S'I*, superior posterior and inferior anterior electrodes

- 1 *L'R*—(*L'*) electrode placed on the posterior chest wall at the level of and grossly parallel to the left border of the heart and (*R*) electrode placed on the anterior chest wall at the level of and grossly parallel to the right border

- 2 RL—Both electrodes placed on the anterior surface of the chest, one (R) at the level of and grossly parallel to the right border of the heart, and the other (L) at the level of and grossly parallel to the left border
- 3 S'I—(S') electrode placed at about the level of the spines of the scapulae on the posterior chest wall and extending practically across it, and (I) electrode situated at the level of and grossly parallel to the inferior border of the heart on the anterior chest wall and extending across it

As in the former investigation, the electrodes were led to a selector switch by means of which any chosen pair could be connected to the standard Lead I contacts of the electrocardiograph. The posterior electrode in each combination was attached to the right arm lead wire of the galvanometer and the anterior electrode to the left arm wire. In the case of Lead RL, in which both electrodes were situated anteriorly, the right electrode was combined with the former and the left electrode with the latter.

The premature contractions were produced by stimulating the ventricles by means of induction shocks from an inductorium, the primary circuit of which was broken by the ordinary Harvard spring interruptor. The latter was so arranged that the number of stimuli per minute was about 10 or 15 in excess of the heart beat. Besides the experimental chest leads, the conventional three leads and Lead IV were generally obtained for each site of artificial impulse formation. In a number of experiments, after the extrasystoles were recorded, the heart was pulled and rotated either to the right or left by means of hooks inserted into the outer wall or by the gloved hand, and then another set of tracings taken under these conditions.

The branches of the Bundle of His were cut according to the method advocated by Roberts et al.⁶ At the end of the experiments (12 in all) the hearts were examined grossly (and in two histologically as well) for evidence of complete transection of the desired branch.

Localization of Site of Origin of Premature Ventricular Contractions by Means of the Experimental Chest Leads Examination of table 1 and figure 2 reveals that consistently the main deflection in Lead RL was upwardly directed when premature contractions were produced from any part of the right ventricle, base or apex, anterior or posterior surface, and downwardly directed in the case of impulses arising from comparable spots on the left ventricle. In Lead L'R the reverse was true, impulses arising from any portion of the right ventricle resulting in negative main deflections, whereas those from the left ventricle produced positive ones. Stimulation of the anterior and posterior aspects of the septum intervening between the outer walls of the ventricles gave variable types of changes in these leads. With Lead S'I, premature contractions originating from any part of the anterior surface of the heart, either right or left ventricle (with the exception of certain instances in the case of the left apex anteriorly), caused the

main wave to be upwardly directed, while stimulation of any portion of the posterior surface, either right or left ventricle, resulted in a negative main deflection. Impulses arising from the lateral surfaces of the right and left ventricles produced changes which fell into either one or the other category or contained characteristics of both. In other words, the main deflection

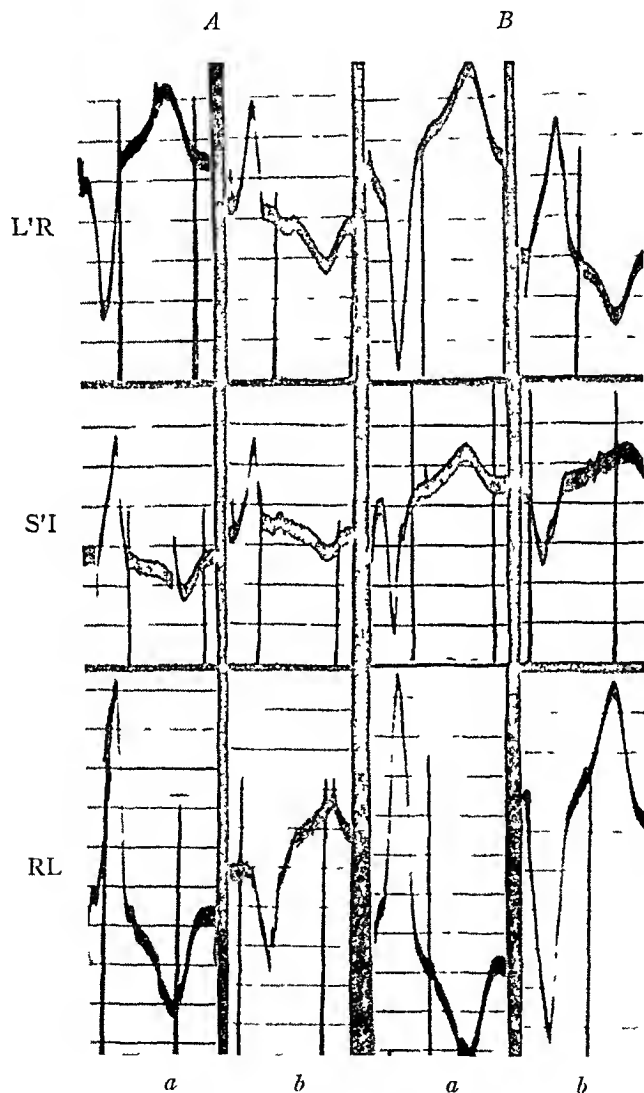


FIG. 2. Curves produced by stimulation of the ventricles. *A* Stimulation of anterior surface of the heart, *a* Right ventricle, *b* Left ventricle. *B* Stimulation of posterior surface of the heart, *a* Right ventricle, *b* Left ventricle.

in Lead S'I in cases of artificial stimulation from these sites was positive or negative, or both positive and negative. As regards the anterior aspect of the apex of the left ventricle, in a number of instances (3 out of 12) the main deflection was downwardly directed. Stimulation of any part of the anterior aspect of the septum consistently produced upright main deflections

in Lead S'I while stimulation of its posterior surface resulted in negative waves. It would therefore appear that the direction of the main deflection in either Lead RL (combination of electrodes on right and left borders of the heart anteriorly) or L'R (one electrode on left border posteriorly and other on right border anteriorly) will localize the site of origin of premature contractions to one or the other ventricle, while the direction of the main deflection in Lead S'I (one electrode on superior border posteriorly and other on inferior border anteriorly) limits it generally to either the anterior or posterior surface of the heart.

Effect of Change in the Position of the Heart on the Direction of the Curves Resulting from Artificial Stimulation. In order to test further the accuracy of the experimental chest leads in localization, a procedure similar to that of Katz and Ackerman⁷ was carried out in the present investigation. In seven instances, the heart was pulled and rotated to the left so that its anterior surface consisted almost entirely of right ventricle, and in six, traction was applied in the opposite direction so as to cause more of the left ventricle to be situated anteriorly. Records of extrasystoles, arising from the two surfaces of the ventricles close to their lateral borders, were obtained before and after the above manipulations and these were compared as to the direction of the main deflection. In nine out of 13 trials a change was noted in Lead S'I. In nearly every instance the alteration in direction could be explained by the fact that the extent of rotation of the heart was usually sufficient to change a previously posterior position to one now anteriorly situated, and vice versa, these results therefore coincided with the differences noted in S'I as one or the other surface was stimulated with the heart in the normal position. In one case, the main deflection in RL was reversed, but in no instance was a change noted in Lead L'R, even in the face of marked rotation and traction of the heart.

In the case of the standard leads and Lead IV considerable alterations were observed following the procedure, the results in these conforming generally to those reported by Katz and Ackerman. In five out of 13 cases the main deflection of the extrasystolic wave was reversed in Lead I and in nine cases, in Lead III. The main deflection in Lead IV was altered in all seven instances in which it was recorded. One can therefore conclude that generally the main deflection in the experimental chest lead which designates the ventricle involved (Lead L'R) is less susceptible to change with alteration in the position of the heart than is the main deflection in the standard leads and Lead IV.

Relative Position of the Electrodes in the Experimental Chest Leads

As in the previous investigation, steps were taken to determine whether or not the most accurate results in localization would be obtained only if the two linear electrodes in the combination were situated on the chest and in a certain definite relationship to each other. Accordingly, various substitutions for one or the other of the two electrodes in Leads L'R (which

TABLE I
Localization of Premature Contractions by Means of the Multi-Plane Chest Leads

Site of Stimulation	Multi-Plane Chest Leads									
	L'R			S'I			RL			
	No of Cases	Main Wave Positive	Main Wave Negative	No of Cases	Main Wave Positive	Main Wave Negative	No of Cases	Main Wave Positive	Main Wave Negative	
Right ventricle, anterior surface	10	0	10	8	8	0	8	8	0	
Left ventricle, anterior surface	10	10	0	12	9	3	7	0	7	
Septum, anterior aspect	2	0	2	3	3	0	2	2	0	
Right ventricle, posterior surface	8	0	8	8	0	8	8	8	0	
Left ventricle, posterior surface	8	8	0	8	0	8	5	0	5	
Septum, posterior aspect	3	0	3	4	0	4	3	3	0	

designated the ventricle) and S'I (which designated surface of heart) were made. These modifications consisted of

- 1 Substituting a large oval electrode situated on the anterior chest wall, so as to overly the heart, for the anterior linear electrodes R and I in Leads L'R and S'I respectively
- 2 Substituting a similar type of electrode placed on a corresponding spot on the back for the posterior linear electrodes L' and S' in the same leads
- 3 Combining first the posterior linear electrode and then the anterior one in each of the two experimental chest leads with an 'indifferent' electrode on the left leg

In the case of the various modifications of Lead L'R employed, it was found that results, which could be utilized for localization of the site of stimulation to one or the other ventricle, were obtained only when the right anterior linear electrode was combined with an 'indifferent' one on the left leg. In all other combinations, inconstant non-specific changes were observed.

In the case of the various modifications of Lead S'I employed, only in those instances in which the anterior inferior linear electrode was combined with a large oval electrode placed on the heart posteriorly were results comparable with those of Lead S'I obtained.

Besides the above, Lead IV was also recorded in order to observe comparable results with a lead in which two relatively large oval electrodes were placed on the chest anteriorly and posteriorly, directly over the heart. Of six instances in which the right ventricle anteriorly was stimulated, in five the main deflection in this lead was upwardly directed while in the remaining one it was negative. In reference to the posterior surface of the same ventricle, in two it was up and in the other two down. In the left ventricle anteriorly, in all instances the main deflection was positive, while in the case of the posterior sites in three it was negative and in one, positive.

To summarize, the most accurate results in localization were consistently obtained when both electrodes in the combination were situated at the estimated borders of the heart. In the case of the modifications of these leads, although some appeared to be equally efficient in localizing the surface and others the ventricle, no one type of combination was of value for both. Lead IV, in which the two electrodes were placed over the heart, was likewise of little use in this respect. On the other hand, with Leads S'I and L'R, both surface and ventricle could be localized in every instance.

Changes Observed in the Experimental Chest Leads Following the Transection of One or the Other Branch of the Bundle of His. The right branch of the Bundle of His was transected in two instances and the left in three. Consistent results were obtained in all experiments. In the case of a lesion of the right branch the main deflection in Leads RL and S'I was

negative while in L'R it was positive (figure 3A) On transection of the left branch, exactly the reverse findings were observed The main deflection in RL and S'I was consistently positive while this wave in L'R was negative (figure 3B)

The deflections in the standard leads conformed to the new classification

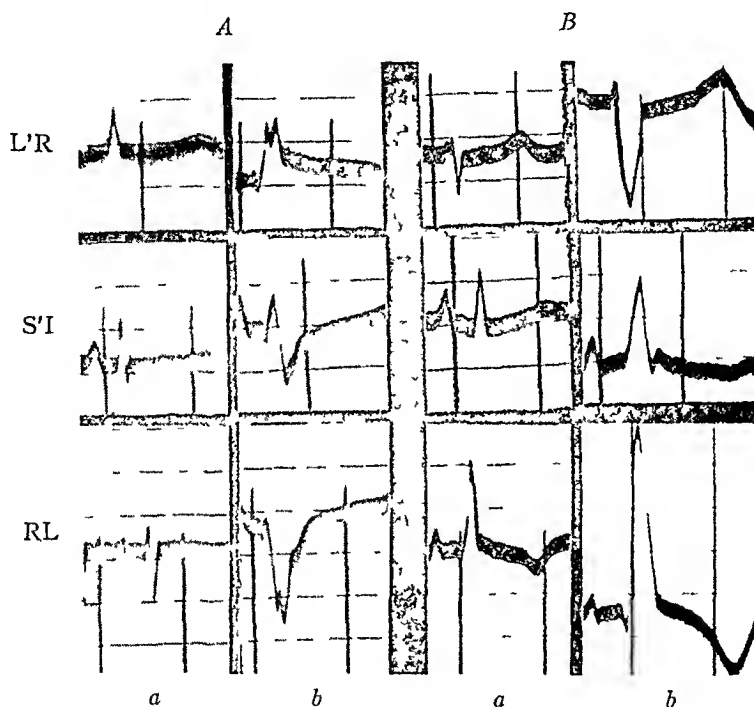


FIG 3 Curves produced by transection of the branches of the bundle of His *A* Transection of right branch, *a* Normal, *b* After transection *B* Transection of left branch, *a* Normal, *b* After transection

of bundle branch block^{6,8,9} while the changes in Lead IV were not characteristic In the latter, the main deflection in both right and left branch lesions was downwardly directed

Comparison of the above findings with those obtained as a result of artificial stimulation of the heart reveals that activation of one ventricle before the other, either because of a bundle branch lesion or because of the origin of the impulse in one ventricle, produces similar types of alterations in the experimental chest leads

SUMMARY AND CONCLUSION

Further evidence is presented to show that certain chest leads, employing combinations of linear electrodes placed parallel to and beyond the estimated borders of the heart, are of considerable value in (1) localizing the site of artificial impulse formation to one or the other surface of the heart as well as to one or the other ventricle, and (2) in designating the branch involved

in experimental bundle branch lesions. The tracings of premature contractions obtained with some of these leads remained unchanged even in the face of sufficient traction and rotation of the heart to produce marked alterations in the standard lead and Lead IV curves.

In view of the consistent results obtained in the present investigation, as well as in the previous one on experimental ventricular cauterizations, it seems reasonable to assume that these experimental chest leads should be of value when applied clinically in the identification and localization of comparable conditions.

REFERENCES

- 1 ABRAMSON, D I, and WEINSTEIN, J. Characteristic variations in combinations of linear chest electrodes (multi-plane chest leads) resulting from experimental ventricular lesions, *Am Jr Physiol*, 1935, cxi, 382-391.
- 2 WEINSTEIN, J. Multi-plane electrocardiography, *ANN INT MED*, 1934, vii, 1503-1512.
- 3 WOOD, F C, and WOLFFERTH, C C. Experimental coronary occlusion, *Arch Int Med*, 1933, li, 771-788.
- 4 WILSON, F N, JOHNSTON, F D, and HILL, I. Interpretation of galvanometric curves obtained when one electrode is distant from heart and other near or in contact with ventricular surface, *Am Heart Jr*, 1934, v, 176-189.
- 5 HOFFMAN, A M, and DELONG, E. Standardization of chest leads and their value in coronary thrombosis and myocardial damage, *Arch Int Med*, 1933, li, 947-964.
- 6 ROBERTS, G H, CRAWFORD, J H, ABRAMSON, D I, and CARDWELL, J C. Experimental bundle-branch block in the cat, *Am Heart Jr*, 1932, vii, 505-513.
- 7 KATZ, L N, and ACKERMAN, W. The effect of the heart's position on the electrocardiographic appearance of ventricular extrasystoles, *Jr Clin Invest*, 1932, xi, 1221-1239.
- 8 WILSON, F N, MACLEOD, A, and BARKER, P S. The interpretation of the initial deflection of the ventricular complex of the electrocardiogram, *Am Heart Jr*, 1931, vi, 637-664.
- 9 WILSON, F N, MACLEOD, A, and BARKER, P S. Order of ventricular excitation in human bundle-branch block, *Am Heart Jr*, 1932, vii, 305-330.

THE EFFECTIVENESS OF ACETYL-B-METHYLCHOLINE GIVEN BY MOUTH AS A VASODILATING AGENT *

By GRACE A. GOLDSMITH, M.D., *Rochester, Minnesota*

CHOLINE and its compounds have been investigated extensively in recent years. Acetylcholine was first prepared by Baeyer in 1867 but remained of chemical interest only until Hunt and Taveau in 1906 noted its marked physiologic activity. Both choline and acetylcholine have been isolated from animal tissues, Dale obtaining the latter in pure chemical form in 1929. Acetylcholine owes its present importance to the almost certain proof that it is the chemical intermediary between parasympathetic nerve stimulation and tissue response (Dale and Alles).

Acetylcholine has three important actions: (1) a parasympathetic effect, inhibiting cardiac action and increasing intestinal tonus, (2) a vasodilating effect, and (3) a nicotine-like effect, causing a rise in blood pressure when its other actions have been abolished by atropine. Acetylcholine has not been useful in clinical medicine as it is rapidly destroyed on contact with blood by enzymic catalyzed hydrolysis.

Acetyl-B-methylcholine was synthesized by Major and his colleagues, and its physiologic properties were tested first by Simonart and later by Comroe and Starr. The effects produced were similar to those caused by stimulation of the parasympathetic nervous system and were accompanied by dilation of peripheral blood vessels. The drug, being less readily destroyed by the body esterases than acetylcholine, was effective when administered orally and subcutaneously.

Starr, Elsom, and Reisinger found that acetyl-B-methylcholine given subcutaneously in doses of 2.5 to 25 mg. caused a fall in blood pressure, a rise in pulse rate, flushing, and sweating. The action began within one minute and lasted from 15 to 20 minutes. Acetyl-B-methylcholine given orally caused a fall in blood pressure, a diminution in the pulse rate, and increased intestinal peristalsis. Effective dosage by mouth was from 50 to 100 times that of subcutaneous injection. The action began 15 to 75 minutes after administration and lasted from a half to one hour. Skin temperature was slightly increased in three of five cases.

Starr gave acetyl-B-methylcholine orally to four patients with Raynaud's disease, with resulting partial relief of the spasm that is excited by mild degrees of cold. One patient with thromboangitis obliterans had a rise in skin temperature of 1.8°C after taking 300 mg. of acetyl-B-methylcholine by mouth. The drug caused temporary reduction in blood pressure in most cases of hypertension in his series.

* Submitted for publication August 16, 1935.
From the Mayo Clinic, Rochester, Minnesota.

Kovacs and Kovacs used acetyl-B-methylcholine by iontophoresis in chronic arthritis and in a few cases of peripheral vascular disease. They obtained an increase in skin temperature in the areas treated which lasted from two to eight hours. Two patients suffering from digital ulcers in cases of Raynaud's disease exhibited rapid healing of the lesions.

Page, who administered this drug subcutaneously to hypertensive patients, found a drop in blood pressure and an increased temperature of the skin of the face and trunk, the hands and feet being almost unaffected. The electrocardiogram often showed an inverted T-wave. The heart rate was increased. Given by mouth in doses of 4 gm the blood pressure was affected little or not at all.

The present study was undertaken to investigate further the effects of the oral administration of acetyl-B-methylcholine (mechoilin)* on the temperature of the skin, pulse rate and blood pressure of subjects who had disease of the blood vessels. The drug was given to 29 patients in doses of 50 to 1500 mg. Experiments were conducted in a room of constant temperature, the subject having rested a half hour or more to allow the blood pressure, pulse rate, and skin temperature to reach a constant level. The temperature of the skin was determined by thermal junctions attached to the fingers and toes. Readings were taken at intervals of 15 minutes for a period of several hours.

EFFECTS OF ACETYL-B-METHYLCHOLINE ADMINISTERED ORALLY

Effect on Skin Temperature The effect of the oral administration of acetyl-B-methylcholine on the temperature of the skin in the cases studied is given in table 1. Any rise of 2°C or less was considered insignificant. Only three patients failed to show such an increase, and of these two received small and insufficient doses. The average maximal rise was 5.82°C and the average high temperature attained in the digits was 33.1°C .

In 13 cases there was a rise of more than 6°C . In cases in which vascular spasm rather than organic occlusion predominated, namely, in cases of hypertension and Raynaud's disease, vasodilation was greatest. Smaller doses (50 to 100 mg) were effective in some instances in cases of Raynaud's disease, whereas in cases of arteriosclerosis and thromboangitis obliterans from 1,000 to 1,500 mg were needed to produce significant vasodilation. In eight cases a rise in temperature occurred in the fingers but none in the toes. Three of these patients received doses of less than 200 mg. Larger doses seem necessary to open up the vessels in the feet. Particularly in Raynaud's disease the fingers were more readily affected.

There was marked variability in the rise in cutaneous temperature in the various digits in cases of Raynaud's disease, and less variability in cases of arteriosclerosis and thromboangitis obliterans. In one case of Raynaud's

* Acetyl-B-methylcholine (mechoilin) for this investigation was furnished through the courtesy of Merck and Company.

TABLE I
Effect of Acetyl-B-Methylcholine on Skin Temperature

Diagnosis	Cases	Maximal rise in skin temperature, degrees C	Actual skin temperature, degrees C
Hypertension	4	Average 6.62 Range 3.1 to 9.6	34.7 33.4 to 36.0
Raynaud's disease and scleroderma	8	Average 7.45 Range 3.0 to 9.9	32.65 27.0 to 35.0
Thromboangitis obliterans	7*	Average 3.67 Range 0.9 to 7.0	32.80 29.6 to 35.6
Arteriosclerosis	5*	Average 4.72 Range 1.0 to 7.3	32.58 27.4 to 35.9
Miscellaneous	5*	Average 6.65 Range 1.5 to 10.5	32.54 26.4 to 36.9
Total	29	Average 5.82	33.11

* In one case in each of these groups there was no appreciable rise in skin temperature (less than 2.0° C)

disease the rise in the temperature of the fingers varied from 1.9° C in one digit to 8.1° C in another. In one case of arteriosclerosis there was a rise of 1.6° C in one toe and of 7° C in another. Organic occlusion of smaller vessels would readily explain this variation. The patients who had hypertension and those of the control group gave evidence of a uniform rise in all digits.

The action of acetyl-B-methylcholine began from 15 minutes to two and a half hours after its oral administration, in 50 per cent of the cases it took effect in from 30 minutes to an hour. The maximal rise in skin temperature usually was attained in from one to three hours. The height of vasodilation was reached in less than one hour in three cases in which small doses were given and in more than five hours in two cases in which 1500 mg of the drug were given. The duration of the rise in cutaneous temperature varied from one to six hours. In seven cases it was more than four hours, and in six additional cases more than three hours. Many experiments were terminated before the temperature returned to the original level. By repeating a dose of 1500 mg in three or four hours vasodilation could be maintained for seven or eight hours. The effect of the drug in a case of thromboangitis obliterans in which the patient was given 1500 mg at the onset of the experiment and four hours later another 1500 mg is shown in figure 1. Seven hours after the first dose the cutaneous temperatures were still considerably elevated. Room temperature remained at 24° C. The other digits behaved similarly. Variations in blood pressure and pulse rate, as can be seen, were too small to be significant.

In three cases a comparison was made between the efficiency of acetyl-B-

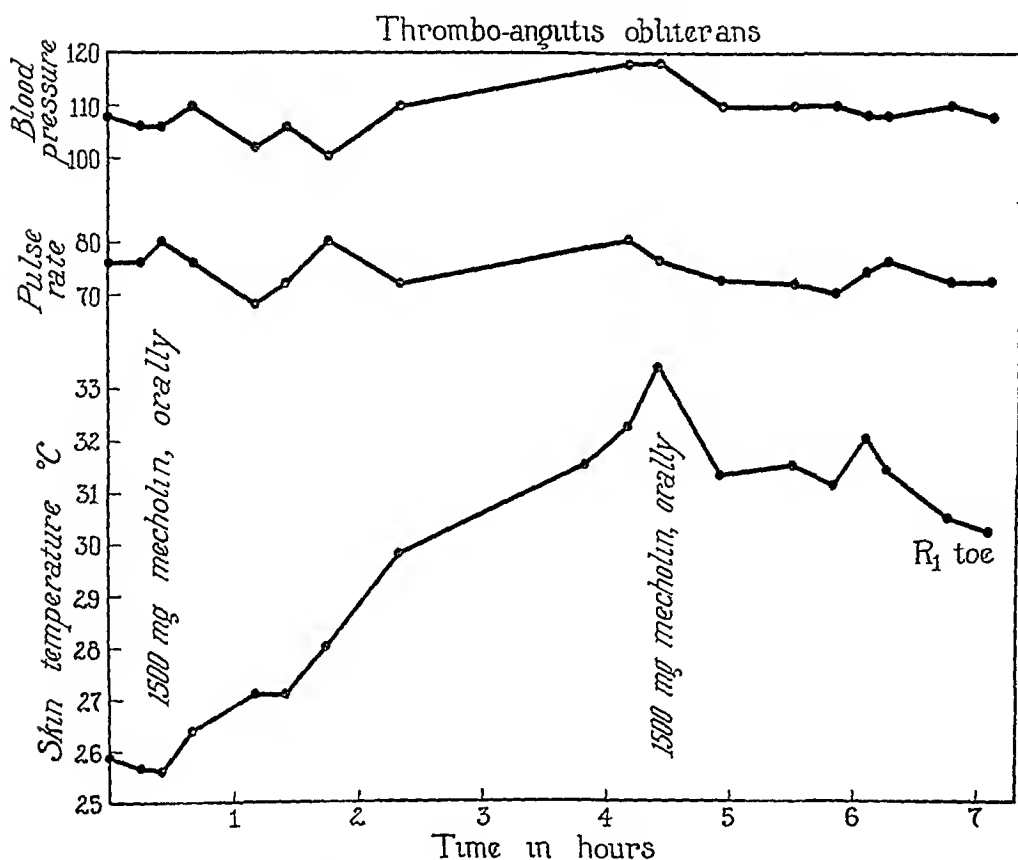


FIG 1 The effect of repeated doses of acetyl-B-methylcholine on skin temperature

methylcholine and typhoid vaccine as vasodilators. If the latter is assumed to be 100 per cent efficient, acetyl-B-methylcholine in these instances averaged 75 per cent in vasodilating ability.

Effect on Exposure to Cold in Raynaud's Disease A patient with Raynaud's disease was given an ice water test to ascertain the effect of acetyl-B-methylcholine on the reaction of the blood vessels in the fingers to exposure to cold. Skin temperatures of the digits were taken until they reached a stable level. The hands were then immersed in ice water at 13.5°C for three minutes. The color reactions were noted, and the temperatures were recorded immediately after removal of the hands from the water and at intervals thereafter. The next day, the entire test was repeated one hour and again two hours after 1 gm of acetyl-B-methylcholine was given by mouth. Changes in color were less marked, and the temperature of the skin did not fall to quite as low a level after the drug had been administered as it had during the control test. In addition to this the hands warmed up much more quickly in the tests performed after acetyl-B-methylcholine had been given and returned to normal in less than 30 minutes, whereas in the control test it took from one to one and a half hours for all the digits to reach their original temperature levels.

Effect on Pain of Peripheral Vascular Disease The administration of acetyl-B-methylcholine did not relieve any of the severe grades of pain in occlusive disease of the blood vessels. Patients with mild discomfort experienced a sensation of warmth and often remarked that their extremities were more comfortable after taking acetyl-B-methylcholine. One patient with ischemic neuritis due to thromboangitis obliterans was given 7.5 gm of acetyl-B-methylcholine in 48 hours without relief from pain. Another patient who had pain caused by an ulcer received 6 gm in 36 hours without relief.

Effect on Intermittent Claudication Acetyl-B-methylcholine was given in two cases in which intermittent claudication was a prominent complaint. The patients were tested by the standard exercise test before the drug was administered and at the height of the ensuing vasodilation. The pain of claudication appeared after the same amount of walking during the control and test periods.

Effect on Blood Pressure Acetyl-B-methylcholine given by mouth had no appreciable effect on the blood pressure in this group of cases. Spontaneous variations in blood pressure, even in a resting condition, are considerable, so any change of less than 15 mm of mercury was not considered significant. Using this standard, 16 of 27 cases showed no change in the systolic and 22 cases no change in the diastolic pressure. Seven cases showed an increase and four a decrease in the systolic pressure. Five cases showed a rise and none a fall in diastolic blood pressure. The disease from which the patient was suffering did not influence the blood pressure as to whether it rose or fell. The response of the blood pressure to the cold test (Hines and Brown) was determined in 10 cases before and at the height of the reaction to acetyl-B-methylcholine. No change was noted.

Effect on the Pulse Rate The pulse rate was observed in 23 of 29 cases. In 14 cases there was no change. In four cases there was a rise of 10 beats or more per minute and in five cases a fall of similar degree. Three of the four patients who showed an increased pulse rate received more than 1500 mg of the drug.

Additional Effects In this series of cases additional effects produced by acetyl-B-methylcholine given by mouth were (1) a sensation of warmth, localized or generalized in 50 per cent of the cases, (2) flushing of the hands or face in 25 per cent, (3) increased perspiration in 20 per cent, and (4) a mild laxative effect, in most of the cases. The only untoward symptoms were mild gas pains and nausea in two cases, one after a small dose of 50 mg and one after 1000 mg of the drug had been given.

EFFECTS OF SUBCUTANEOUS ADMINISTRATION

Acetyl-B-methylcholine was given subcutaneously to two patients who had hypertension and to one patient who had thromboangitis obliterans. The typical effect of a dose of 20 mg was an immediate and marked fall in

systolic and diastolic blood pressure, a rise in pulse rate, flushing of the face, sweating, and salivation. Nausea and substernal pain were noted in one case. There was a fall in the temperature of the skin of the feet which was probably a compensatory phenomenon. The action began within two minutes after injection and lasted 30 to 45 minutes.

The differences in the effects of subcutaneous and oral administration of the drug are striking. When taken by mouth, the vasodilating action predominates and there is little influence on blood pressure and pulse rate. Large doses are needed and the reaction is slow and prolonged. Subcutaneous administration affects primarily the blood pressure, causing uncomfortable side actions of sweating, salivation, and nausea, the action being rapid and evanescent.

° SUMMARY AND CONCLUSIONS

Acetyl-B-methylcholine administered orally to 29 patients in doses of 50 to 1500 mg. caused an average maximal rise in the temperature of the skin of the digits of 5.82°C . Vasodilation failed to occur in only one case in which an adequate dose was given. The vasodilating effect of acetyl-B-methylcholine varies tremendously with different patients, in different pathologic conditions and in the different digits of a given individual.

The vasodilation resulting from the oral administration of acetyl-B-methylcholine is slow in onset and is of relatively long duration. An adequate dose seems to be between 1000 and 1500 mg., and this dose may be repeated every three or four hours to maintain vasodilation. No untoward results have followed the administration of 3 to 4.5 gm. in 24 hours.

No significant changes were produced in blood pressure or pulse rate in the cases studied.

Acetyl-B-methylcholine seems to be a promising drug for use in peripheral vascular disease because of its vasodilating properties, its prolonged action, its safety, and its ease of administration. The clinical use of this drug is limited at present owing to its relatively high cost.

BIBLIOGRAPHY

- 1 ALLES, G. A. The physiological significance of choline derivatives, *Physiol. Rev.*, 1934, **xiv**, 276-304.
- 2 BAEYER. Quoted by Alles.
- 3 COMROE, J. H., JR. and STARR, I., JR. Further studies on the pharmacology of acetyl-B-methylcholine and the ethyl ester of B-methylcholine, *Jr. Pharmacol. and Exper. Therap.*, 1933, **xix**, 283-299.
- 4 DALE, SIR H. Chemical transmission of the effects of nerve impulses, *Brit. Med. Jr.*, 1934, **i**, 835-841.
- 5 HINES, E. A., JR., and BROWN, G. E. A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state, *ANN. INT. MED.*, 1933, **vii**, 209-217.
- 6 HUNT and TAYLOR. Quoted by Dale.
- 7 KOVACS, R., and KOVACS, J. Newer aspects of iontophoresis for arthritis and circulatory disturbances, *Arch. Phys. Therap.*, 1934, **xi**, 593-598.

- 8 MAJOR Quoted by Alles
- 9 PAGE, I H Acetyl-B-methylcholine (mechoin) , observations concerning its action on blood pressure, skin temperature and heart, as exhibited by electrocardiogram of hypertensive patients, Am Jr Med Sci , 1935, clxxxx, 55-64
- 10 SIMONART Quoted by Alles
- 11 STARR, I, JR Acetyl-B-methylcholine III Its action on paroxysmal tachycardia and peripheral vascular disease, with a discussion of its action in other conditions, Am Jr Med Sci , 1933, clxxxvi, 330-345
- 12 STARR, I, JR, ELSOM, K A , and REISINGER, J A Acetyl-B-methylcholine I The action on normal persons, Am Jr Med Sci , 1933, clxxxvi, 313-323

BLACKWATER FEVER. A CLINICAL REVIEW OF FIFTY-TWO CASES¹

By M. FERNÁN-NÚÑEZ, M.D. (Madrid), *Milwaukee, Wisconsin*

THE conquest of the diseases of the tropics by modern medicine has been one of the most dramatic applications of science during the progress of civilization. The causative agent of practically every tropical disease has been discovered and an effective sanitary protection and specific treatment provided against each one.

The population pressures and economic difficulties of life in the more crowded countries of the world demand that the fertile and sparsely peopled tropical lands be made available for settlement. In the tropics there still remains one major disease, hemoglobinuric fever, which is the terror of the white man. To it an enormous amount of research has been devoted with but little addition to our knowledge of its etiology and therapy.

The objective of this paper is to emphasize a different line of investigation which offers a promise of affording insight into the mechanism of this terrible malady, and to restate briefly most of the important established facts concerning it, giving to the whole an interpretation based upon the experience of the writer in the treatment of 52 cases of hemoglobinuric fever and the observation of as many more patients of other practitioners in tropical practice.

This disease syndrome has received various designations: Hemoglobinuric Fever, Blackwater Fever, Hemorrhagic Malarial Fever, Black Jaundice, Canebroke Yellow Fever, etc. The descriptions in the literature indicate that it has often been confused with the bilious types of malaria, with yellow fever, with the icteroid manifestations of various spirochetal infections (icterohemorrhagic fever, relapsing fever, dengue, etc.) and with toxic and symptomatic hemoglobinurias.

Early accurate clinical descriptions of it were written by physicians in New Orleans (1832), Georgia (1835), the Wabash River valley of Indiana (1837), the White River valley of Illinois (1843), and subsequently in the Great Lakes region and Canada, the Pacific coast, New Jersey, Pennsylvania, New York, Connecticut and Rhode Island.

Since its discovery in the United States and Europe it has become more frequent in the tropics due to the increased migration there of the white races, in which it is chiefly found. Its incidence and geographical distribution parallel exactly those of estivo-autumnal (malignant subtertian) malaria, of which the *Plasmodium falciparum* is the known causative agent.

* Received for publication November 23, 1935.

ETIOLOGY

With a disease so spectacular in its manifestations and mortality, and in which no specific causative agent has yet been discovered, it is quite natural that many theories should have arisen to explain it.

The Malaria Theory The disease appears only in malarial districts and in persons who are being treated for malaria, its ratio corresponding almost exactly to the percentage of estivo-autumnal malaria in a community.

The Quinine Theory The attacks often follow immediately on the taking of quinine, and sometimes the patient's condition improves on the stoppage of quinine.

The Allergic Theory The present writer believes that blackwater fever is merely an allergic manifestation of malaria in which quinine, exposure and various other resistance-reducing agencies aid in precipitating the attack. It occurs chiefly in Europeans who have had one or more attacks of estivo-autumnal fever during a residence usually of at least two years in the tropics. In such an individual sensitized by previous attacks a new attack of estivo-autumnal malaria or the administration of quinine in a latent case brings on the acute syndrome by the liberation of allergens.

The author's intradermal test with suspensions of *Plasmodium falciparum* rendered non-infective (Plasmodoid) was applied in a group of persons of Caucasian extraction who had resided in an endemic area of Colombia for more than six months. Following the removal of those showing a positive sensitivity, blackwater fever disappeared from that area.

SYMPTOMS

In typical cases the patient suffers a sudden attack which resembles a rather severe paroxysm of malaria with chill, fever, sweat, headache, and more marked exhaustion than accompanies the usual malarial attack. This is followed by hemoglobinuria. The patient is greatly depressed and very ill. The mind is clear but there is restlessness and anxiety. In favorable cases improvement is observed on the second day.

Urine The fresh urine contains oxyhemoglobin, an increase in urobilin, an unknown pigment (hemozoin?), and a marked albuminuria. Upon standing methemoglobin quickly forms and the urine turns black (blackwater). Red cells are absent and the fresh urine is usually clear, not smoky as when unaltered blood is present. The specific gravity is around 1.025. On shaking the foam is pinkish in color. The reaction is markedly acid and acetone bodies are present. There are granular and pigmented casts. In the average case the hemoglobin in the urine is equal to that in 300 c.c. of blood, but the red cell destruction is often many times as great as the amount of blackwater would lead us to suppose, since much of the pigment is broken down or deposited in the reticulo-endothelial system throughout the body.

Often in the ambulant type the first intimation the patient has that anything is the matter is the passing of black urine. He may feel extraordinarily well and pyrexia may be absent, but the pulse rate is usually increased¹. At times hemoglobinuria may be entirely absent, due to the breaking down of the pigments by the reticulo-endothelial system, or it may appear on and off. Specimens should be collected in separate containers at different time intervals.

Fever The fever at the beginning is usually around 101° F but may run up to 104° or 105° F quickly, then subside somewhat after the sweat, but does not always return to normal, being continuous or remitting, and at times resembling the temperature curve of spirochetal relapsing fever. In atypical (ambulatory) cases the temperature may be subnormal.

Jaundice This comes early, is intense and appears at the same time as the hemoglobinuria. Being a hemolytic jaundice it differs from the obstructive type in that there is no retention of bile salts in the blood. Itching of the skin is not marked, there is no bradycardia, no prolongation of the coagulation time and no hemorrhages due to injury of the capillary endothelium by bile salts.

Vomitus This is "leafy green" and accompanied by epigastric distress. The feces always give the reaction for occult blood, and in severe cases blood and hemoglobin may be passed per anum, as in dysentery.²

The *pulse* is rapid, 110 to 150 per minute, feeble and of low tension, in severe cases resembling that of shock. It differs thus from the slow pulse of yellow fever and obstructive icterus.

Blood Within 24 hours the erythrocytes may be reduced to 2,500,000 and later in the attack to 1,000,000 per cu mm. The hemoglobin is correspondingly decreased, but hemoglobin estimations are very inaccurate since the plasma is deeply colored with free hemoglobin. The leukocyte count shows an increase in the phagocytic melaniferous monocytes (up to 24 per cent), which is explained by their being a part of the reticulo-endothelial system. The sedimentation time is decreased, and there is reduction in the coagulation time.³ During the first 48 hours approximately 20 per cent of cases show malarial parasites in the blood, chiefly subtertian rings, which usually rapidly disappear.

Five c.c. of blood placed on ice for 5 minutes, then incubated at 37° C for one hour, show no hemolysis, thus differing markedly from the blood in paroxysmal hemoglobinuria ("autolytic reaction").⁴

The *spleen* is enlarged and tender. Tissue smears from the splenic pulp and rib marrow reveal parasites in 30 per cent of cases.²

Anuria is the most feared complication. It is practically complete, but the patient remains perfectly *compos mentis* and with no edema for 12 to 14 days, and then dies after a few hours of increasing unconsciousness. Patients seldom recover if the suppression lasts more than 24 hours.

Antecedent abdominal disease is apt to light up. Appendicitis, intus-

seption, gastritis, cholecystitis, severe colics, relapse of amebic dysentery, obstinate constipation may occur

Relapses are exceedingly common in cases which have moved or been moved, or are even restless in bed, in from 48 to 72 hours, and such relapses may be more than six in number, each one leaving the patient in a weaker state. Cases moved are liable to very sudden and alarming jaundice. Severe anemia and nephritis increase the tendency to relapses.¹

PATHOLOGY

Few reports of systematic postmortem studies of hemoglobinuric fever cases are available and our knowledge of the pathognomonic pathology is rather meager. Necropsies are usually performed 8 to 10 days after the beginning of an attack and, as death is then due to anemia or urinary suppression, these examinations may show little evidences of malaria. The writer performed autopsies on 11 cases of fatal blackwater fever and the observations are here summarized.

In 20 per cent of cases of estivo-autumnal malaria one ordinarily finds in the peripheral blood only the early ring forms of schizonts and the gametocytes (crescents). The later stages of schizogony are carried out in the internal organs. The large segmenting forms are held in the capillaries by the reticulo-endothelial cells, which accounts for their tendency to agglutination with occlusion of vessels supplying important organs, and explains why the pernicious forms of malaria (comatose type, etc.) are found chiefly in malignant tertian.

During the anaphylactic attack which initiates the hemoglobinuria the parasites are destroyed along with the parasitized red cells, parasites rarely being found in great numbers during the illness or postmortem, but the pigment from the parasites remains and is deposited in the reticulo-endothelial cells of all organs of the body.

The *kidneys* are swollen and the surface is a deep red or mottled red and yellow. The cortex is widened and ecchymotic due to the hemoglobin in the tubules, and yellowish if the jaundice is severe. The pyramids are a deep purple color and sometimes show minute hemorrhages.

Microscopically the glomerular tufts show thromboses of degenerated parasites and pigment. There is cloudy swelling of the tubular epithelium which contains great quantities of hemosiderin, as shown by the Prussian-blue reaction. The tubules, especially the loops of Henle, are obstructed with hemoglobin, agglutinated erythrocytes and epithelial casts, the markedly acid urine favoring coagulation of the hemoglobin.

The *spleen* weighs 400 to 600 grams, is very friable, and presents a soft bright red or purple velvety pulp. Its capsule is smooth and thin. The malpighian corpuscles are grossly opaque and well outlined.

The splenic sinuses are distended with blood and agglutinated cells with marked phagocytosis of the red cells by the reticulo-endothelial elements.

Malarial pigment is usually abundant. The Prussian-blue reaction for hemosiderin shows focal necrosis due to infarction.

If there has been chronic malarial splenomegaly the spleen will be slaty or jet black due to the large amount of pigment, and the walls of the blood vessels will be thickened.

The *liver* is enlarged, of a pale chestnut brown color and shows focal necroses of toxic origin. The sinusoids are dilated and erythrocytes are seen agglutinated around the Kupffer cells. The hepatic cells, especially around the central vein, show increase in the albuminous granules. Small hemorrhagic areas are present in the midzonal region of the hepatic lobules. The Prussian-blue reaction for free iron is intense.

The bile is usually very thick in the gall-bladder due to the sudden and enormous destruction of red cells and some times may be turned out as a solid mass. In ordinary malaria the hemolysis is not sufficiently intense to lead to formation of pigment concretions but in hemoglobinuric fever inspissated nodules may quickly form and cause symptoms of cholelithiasis. The gall-bladder wall shows no changes referable to the blackwater fever itself except deep pigmentation of the mucosa.

The *brain* is pale and waxy. On microscopic examination it may show edema and various capillaries filled with malarial pigment and hemoglobin. Hemorrhages and thrombi are sometimes seen. There is no staining of the brain substance by the jaundice as is notable in the other tissues of the body.

The *heart muscle* is soft and flabby and microscopically shows swelling of the muscle cells, considerable loss of striation, deeply staining nuclei, albuminous and fatty degeneration.

The *bone marrow* is usually hyperplastic as a result of the anemia, and its vessels and macrophages contain much pigment.

The mucosa of the *stomach and intestines* shows marked discoloration due to hemoglobin.

There is rather intense yellowish discoloration of all the tissues of the body, due to the presence of bile pigment in the blood plasma.

DIFFERENTIAL DIAGNOSIS

Paroxysmal hemoglobinuria may be impossible to differentiate from hemoglobinuric fever. It is much more common in cold climates and should always be suspected when cases of the latter disease seem to appear in non-malarial districts. There is practically always a definite history of chilling of the body immediately preceding the paroxysm. The patient is usually in much better general health and recovers from the attack much more quickly than is common in blackwater fever. It is never fatal.

Yellow Fever. On the fourth day hematuria (not hemoglobinuria) with smoky urine, and progressive jaundice begin and "black vomit" appears. Faget's sign, high temperature (104° F) with slow pulse (60), is observed. The spleen is not enlarged.

Bilious Malaria The urine is yellowish (bile) The jaundice is not so intense and the yellowish vomitus not so dark as in yellow fever or hemoglobinuric fever The pulse is slower than that seen in the "shock" (anaphylactic?) of blackwater fever There is usually marked splenomegaly (up to 1000 grams)

PROGNOSIS

An individual healthy in other respects usually recovers, provided he is correctly treated and *submits to it* With urinary suppression the prognosis is extremely bad Persistent vomiting, hiccough and relapses are ominous The general mortality is 20 to 30 per cent

TREATMENT

Blackwater fever must be thoroughly and carefully treated from the very beginning and to the end of the illness Good treatment, including good nursing, saves lives in this disease Early apparent improvement should not lead to slackening of treatment—relapses are common and dangerous! When the patient has recovered he should change his residence to a healthful climate as he will be prone to subsequent attacks which might cost him his life

After experience with all the accepted methods of treatment the routine here given was adopted

Nursing The patient should be put to bed and *not moved* lest his hemoglobinuria increase, or, if already stopped, recur Absolute rest in bed with good nursing is essential Avoid chilling, eliminate unnecessary noise, keep visitors away, and use every possible means to keep the patient quiet From the first moment push fluids and nourishment (barley water, albumin water, broths, fruit juices, glucose, etc.) Do not allow a return to normal diet until convalescence is well advanced, as hemoglobinuria may reappear

The weakened heart muscle requires that the patient be kept in absolute relaxation for three to six weeks after the acute attack Then he may be allowed up very slowly At the end of the second week permit an additional pillow a day until the patient is sitting up, and very gradually allow him out of bed Lack of care in this matter will often bring on a relapse and may cost the life of the patient

Arsphenamines The writer found the use of the arsphenamines so superior to quinine that he practically abandoned the latter in this disease Neoarsphenamine ("914"), 0.2 gram in 2 c.c. of sterile distilled water, by vein often gave spectacular relief if used early in the disease Thereafter weekly injections of 0.2 to 0.4 gram proved of great aid in combating the severe anemia and strengthening the patient during convalescence Neoarsphenamine is possibly contraindicated in patients showing signs of toxic necrosis of the liver

A freshly prepared solution of 5 grains (0.325) of sodium thiosulphate (hyposulphite) in 5 c.c. of sterile distilled water should be injected intravenously (through the same needle used for the "914" while in place). This will prevent any untoward effects of the neoarsphenamine without impairing its therapeutic efficiency.

Sodium thiosulphate apparently has a very specific effect on the hemoglobinuria, often stopping it within a few hours. If preferred, the drug may be given by mouth in 10 to 30 grain (0.6 to 2.0 grams) doses daily.

Acidosis As many of the features of the attack suggest acidosis, and a condition of acidosis seems to favor hemolysis, it has been the author's custom to use intensive alkali therapy routinely. Sodium bicarbonate, 300 to 500 c.c. of a 2 per cent solution, is given intravenously daily. As the bicarbonate changes to the carbonate on prolonged heating it is best to sterilize the solution at 7 pounds pressure in a live-steam autoclave. If this is not convenient the water should be boiled, allowed to cool down to near the desired temperature for injection, and the bicarbonate added. A dilute (0.5 of 1 per cent) bicarbonate solution may be given also by the Murphy drip.

Glucose, 300 c.c. of a 5 per cent solution, daily by vein, and additional quantities by the Murphy drip are useful in combatting the acidosis and general toxemia and in nourishing the patient.

Anuria The sodium bicarbonate and glucose solutions administered as above will aid in increasing the flow of urine and by thus eliminating the products of hemolysis from the blood shorten the period of hemoglobinuria. Early injections, before the anuria appears, may prevent the suppression. High enemas, as hot as can be borne, with a return flow tube, are often of great aid in starting the urinary flow since they bring heat directly to the splanchnic area. For the pain resulting from renal congestion hot fomentations applied to the loins are often very efficacious.

Vomiting Alkaline waters (0.5 of 1 per cent solution of sodium bicarbonate) may be freely used. Carbonated beverages (ordinary "soda-pop") are often better tolerated by the patient than anything else, and the sugars they contain are nourishing. Iced lemonade is usually well borne. Morphine and atropine may be required.

The rapid dehydration caused by vomiting may need to be combated by saline transfusions (intravenous drip is especially useful), or 300 c.c. may be introduced high into the bowel through a rectal tube every four hours.

Magnesium citrate or other mild saline laxatives daily are usually tolerated and are very necessary for cleansing the intestines of the bile and toxins. During convalescence calomel in fairly large doses (5 grains), followed by a saline laxative, is especially indicated in clearing up the jaundice.

Stimulants All forms of alcohol should be avoided.

Caffeine sodiobenzoate, 3 grains (0.2) twice daily, intramuscularly, stimulates the weakened heart and promotes diuresis. Adrenalin, 8 minims, (0.5 c.c.) of a 1/1000 solution, is administered intramuscularly at once and

every three hours until a total of four doses is given. This may be repeated on the second day of the disease if hemoglobinuria persists. Aside from its aid in relieving hypotension, it has a specific effect in relieving the anaphylactoid symptoms. Ephedrine in equivalent dosage, subcutaneously or orally, can be tried instead of adrenalin.

Quinine If neoarsphenamine is not available quinine administered as here outlined may be substituted. The hemolysis of the attack causes auto-destruction of the malaria parasites in 70 per cent of cases. Quinine should only be administered in those 30 per cent of cases still showing parasites in the peripheral blood. Five grains are given the first day by mouth or intramuscularly, 10 grains (0.65 gm.) the second day, 15 grains (1.0) the third day and thereafter. After convalescence, if malarial parasites are still present in the peripheral blood, quinine may be cautiously given, watching for a return of the hemoglobinuria.

Quinine idiosyncrasy should always be tested for. Inject 1 gram (0.065 gm.) of quinine dihydrochloride or bisulphate. If there is no reaction in an hour, inject 4 grains (0.25). If there is quinine hypersensitiveness this will almost surely produce a reaction. If the reaction is slight, the injection is repeated in 12 hours, otherwise it is postponed for 24 hours. The injections are continued daily until the malaria is cured. To avoid abscesses the injections should be given intramuscularly in a dilution of 1 gram in 1 c.c. of sterile water, and the skin at the site of injection thoroughly sterilized.

It is extremely doubtful whether plasmochin (plasmoquin) should ever be used in blackwater fever, except possibly in cases where there is a quinine idiosyncrasy. This drug is highly toxic, affecting especially the liver, and often causes cyanosis and hemoglobinuria in itself. Its action on the subtertian parasites is not nearly as effective as it is on the tertian. If employed at all, not over 0.03 gram, twice daily, intramuscularly, should be administered to hold the infection under control until the acute stage of hemolysis has subsided and quinine can be more safely given.

Atebrin, orally in 0.3 gram doses daily, for three doses, may be tried instead of plasmochin. As it colors the urine and skin yellow it may appear to make the disease worse.

Other Drugs Our somewhat limited experience with the following measures did not convince us of their general utility. For anuria—tincture of cantharides (Trout), bichloride of mercury (Hearsey), cyanide of mercury, novasural and salyrgan. For hemoglobinuria—calcium lactate (Castellani), hemostatic serum (Aguilar), *Streptococcus hemolyticus* antiserum (Crawford), Bothropic antivenin (Makel) and cholesterin.

Blood transfusions in six cases left us uncertain as to their value. If used at all we would urge a careful direct matching of the bloods of the recipient and donor and repeated transfusions of small amounts (100 c.c.)

CONCLUSIONS

1 Blackwater fever is practically the one remaining tropical disease whose etiology has not been definitely solved

2 The theory is submitted that it is an allergic manifestation of estivo-autumnal (malignant subtertian) malaria

3 Reference is made to the author's intradermal test for the detection of individuals allergic to estivo-autumnal malaria, who if attacked again by the disease would be potential victims of hemoglobinuric fever

4 The symptoms, pathology and treatment of blackwater fever are reviewed on the background of the writer's experience in the personal management of 52 cases of the disease and the observation of an equal number of patients of other physicians

BIBLIOGRAPHY

- 1 CARMODY, E P Blackwater fever, Jr Med Assoc of South Africa, 1929, III, 389-390
- 2 MAKEL, H P, and GILDER, W Blackwater fever, The Military Surgeon, 1930, 156-164
- 3 MENK, W Blackwater fever in the Banos Hospital (Cuba), Annual Report United Fruit Co Med Dept, 1927, 113-117
- 4 STITT, E R Diagnostics and treatment of tropical diseases, 5th Ed, P Blakiston's Sons & Co, Philadelphia
- 5 TODD, J C, and SANFORD, A H Clinical diagnosis by laboratory methods, 7th Ed, 319-321, W B Saunders & Co, Philadelphia
- 6 TACIO, A A, and ROJAS, M D The treatment of hemoglobinuric fever with caffeine sodio-benzoate, Jr Trop Med and Hyg, Liverpool, (March 18) 1925
- 7 WHITMORE, E H Blackwater fever, ANN INT MED, 1928, 316-324
- 8 BRAHMACHARI P, et al Studies in blackwater fever, Jr Trop Med and Hyg, 1932, 309-310
- 9 GHIRON, M On blackwater fever, Jr Trop Med and Hyg, 1932, 65-71
- 10 STEPHENS, J W W Ann Trop Med and Parasit, Liverpool, 1929, 451-479
- 11 STEPHENS, J W W Proc Internat Conf on Blackwater Fever, Boston, 1925, I, 121-128
- 12 BLACKLOCK, B Etiology of blackwater fever, Pub Sir Alfred Lewis Jones Research Lab, Freetown, (Feb 5) 1923
- 13 BLACKLOCK, D B, and MACDONALD, G Mechanism of blackwater fever and certain allied conditions, British Med Jr, 1928, 145-149
- 14 LOW, G C Blood transfusion in blackwater fever, Lancet, 1928, 645-647
- 15 WHITMORE, E R, and ROE, J H Further study of the blood in blackwater fever, Annual Report United Fruit Co Med Dept, 1929, 59-64
- 16 BODFCHTEL, G Ein Beitrag zur Frage de Übertragbarkeit der menschlichen Malaria auf Versuchstiere, Klin Wchnschr, 1930, 2020
- 17 ALESSANDRO, A L'adrenalina nella cura della splenomegalia malarica cronica, Riv Sanitaria Siciliana, 1932, 332, 335-338, 341-342
- 18 GARNHAM, P C C Observations on *Plasmodium falciparum* with special reference to the production of crescents, Kenya and East African Med Jr, 1931, VIII, 2-21
- 19 CHESTERMAN, C C Treatment of blackwater fever by oral sodium bicarbonate, Lancet, 1929, 1355-1356
- 20 TOLLESON, H M Treatment of hemoglobinuric fever, Jr Ga Med Assoc, 1930, XI, 53-57
- 21 DEL VALLE, C M A case of blackwater fever and its urologic aspect, N Y State Jr Med, 1930, XXX, 1287-1288

- 22 FAIRLEY, K. D. Cholelithiasis as a sequel of blackwater fever, *Lancet*, 1930, 1395-1396.
- 23 MILANI, C., and CUBONI, E. Inoculation de la malaria chez l'homme et immunité antimalarique, *Boll. Sezione Ital. Internaz. di Microbiologia*, Milan, III (Sept.) 1931.
- 24 PATERSON, J. C. The value of plasmochin in the treatment of malaria infections countered in some cases of blackwater fever and quinine hemoglobinuria, *Am. J. Trop. Med.*, 1932, **1**, 363-368.
- 25 WAKEMAN, A. M., MORRELL, C. A., EISENMAN, A. J., SPRUNT, D. L., and PETERS, J. The metabolism and treatment of blackwater fever, *Am. J. Trop. Med.*, 1932, **1**, 440.
- 26 Note—L'idiosincrasia chininica e la sua cura, *Riforma Med.*, 1932, **4**, 1115-1116.
- 27 BRAHMACHARI, U., BRAHMACHARI, P., and BANERJEE, R. Studies in blackwater fever, *Am. J. Trop. Med.*, 1932, **1**, 117-122.
- 28 MANWELL, R. Quinine and plasmochin therapy in *Plasmodium* infections and other avian malarías, *Am. J. Trop. Med.*, 1932, **1**, 123-146.
- 29 PATERSON, J. C. Note on the use of alkali therapy in the treatment of blackwater fever, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1933, **27**, 6.

THE TREATMENT OF NARCOLEPSY WITH BENZEDRINE SULPHATE *

By HELMUTH ULRICH, M D, F A C P, CARL E TRAPP, M D, and BEN VIDGOTT M D, *Boston, Massachusetts*

INHALATION of benzedrine (synthetic racemic benzyl-methyl carbinamine $C_6H_5CH_2CHNH_2CH_3$,¹) for the relief of nasal congestion was found by one of us to be followed by sleeplessness, an experience that suggested the use of this method in the treatment of narcolepsy. Clinical trial showed, however, that inhalation of the drug produced very slight results, whereas oral medication was uniformly successful in preventing narcoleptic seizures. Six cases of narcolepsy have been treated by us and form the basis of this report. Prinzmetal and Bloomberg,² also, in a recent report published since the inception of our study, found oral treatment with benzedrine to give complete relief in nearly all of their cases.

Narcolepsy is a disease characterized by recurring attacks of diurnal sleep †. In many cases there occur also periods of muscular atony or helplessness (cataplexy). The fundamental nature of the disease is not understood. It is possible that the underlying defect is often congenital and that infections and other exciting causes (trauma, etc.) act as precipitants.³ There is no convincing evidence, however, that the disease is hereditary or familial. It is believed by some to be the result of disturbance in the region of the basal ganglia (thalamus,^{4, 5} floor of third ventricle³), although other portions of the brain also have been incriminated. In several reported cases of narcolepsy, the onset followed acute infectious disease, especially influenza and encephalitis.³ Trauma⁶ and over-exertion⁷ also have been held responsible in a few instances. Attempts have been made to incriminate the endocrine glands, chiefly the pituitary,⁸ because a tendency to obesity has frequently been observed to develop simultaneously with the onset of narcolepsy and also because in many cases the somnolence had its initial appearance in the years of adolescence.⁵ A few cases have developed at the menopause. No age is exempt, although in the majority of the reported cases the onset of the disease occurred before the age of twenty-five.

The fact that six cases were admitted to the Evans Memorial within a period of one year indicates that the disease occurs with increasing frequency. It is chronic and usually incurable,⁹ although spontaneous amelioration has been noted in several untreated cases, and the condition does not preclude a long and otherwise healthy life.³ Symptoms and signs other than diurnal somnolence and loss of muscular tone include disturbed nocturnal sleep (insomnia, unpleasant and often terrifying dreams), irri-

* Received for publication January 8 1936

From the Evans Memorial of the Massachusetts Memorial Hospitals, Boston, Mass.

† For a detailed discussion and comprehensive bibliography of narcolepsy the reader is referred to Daniels' excellent thesis.³

tability, nervousness, obesity, dermatographia, diminished libido, and a low basal metabolic rate. The disturbance of nocturnal sleep appears to be the most common. The other symptoms are said to occur with varying degrees of frequency.

Several forms of treatment have been recommended, including psychotherapy, endocrine medication (thyroid, pituitary), caffeine, and especially ephedrine sulphate, which was used first by Janota.¹¹ None of these, with the exception of ephedrine sulphate, has been notably successful.

Benzedrine is closely related to ephedrine but, according to Alles¹² has a more marked effect as a stimulant of the central nervous system. In the series of six cases reported herewith, consistently good results were obtained with the oral use of benzedrine sulphate.¹

Case 1 Mrs M F, an American housewife, aged 52, entered the hospital on March 4, 1935, with the chief complaint of falling asleep during any monotonous procedure such as riding in an automobile, listening to a sermon, etc. The onset was three years ago. The attacks of sleep were more frequent after meals, shortly after getting up in the morning, and in extremes of heat or cold (very cold winter days or a very warm room). The duration of an attack was a few seconds to several minutes. On one occasion, she fell asleep while mixing dough and continued the operation throughout the narcoleptic attack. At times she took part in a conversation during an attack. A slight stimulus was sufficient to awake her. Prodromal symptoms consisted of diplopia and a dull feeling in the eyes.

In addition to the narcoleptic seizures, she had attacks of loss of muscular tone that were usually brought on by excitement or hearty laughter. If she was standing, she fell to the ground unless a support was at hand to lean against. During these cataplectic attacks she was fully conscious, but could not move. They lasted a few minutes and were not followed by any unpleasant sensations. Nocturnal sleep was poor and often disturbed by unpleasant dreams.

The family history was not remarkable. The previous personal history revealed that she had measles and pertussis in childhood, chicken-pox at age 21, and mumps at age 25. A year ago, a diagnosis of gastric ulcer had been made because she complained of gas and distress after meals. The menstrual history was normal. The last period occurred six months ago. She was nervous and irritable and tired easily.

There was moderate generalized obesity, the present and highest weight being 169 pounds. She had always been slightly obese, but a marked increase in weight began with the onset of narcolepsy. The teeth were in poor condition. Examination of the ocular fundi revealed moderate vascular sclerosis and an enlarged optic spot. Pelvic examination disclosed hypertrophy, bilateral laceration and inflammation of the cervix of the uterus. Otherwise physical examination was negative.

The systolic blood pressure was 132 mm mercury, the diastolic 86 mm. The urine contained a slightest possible trace of albumin and was otherwise normal. The blood count revealed slight anemia (hemoglobin 78 per cent, erythrocytes 3,970,000), but was otherwise normal. The non-protein nitrogen was 31 mg, uric acid 3 mg, sugar 100 mg, calcium 11.5 mg, and phosphorus 2.4 mg in 100 c.c. of blood. The Wassermann and Kahn tests were negative. The basal metabolic rate was minus 24 per cent. Cerebrospinal fluid: The fluid was slightly tinged with cells, other than blood discs, numbered 21 per cu mm, the sugar was 67 mg per 100 c.c., the Wassermann test was negative. Roentgen-ray examinations of the skull were normal.

* The benzedrine sulphate used in this study was supplied by Smith, Kline and French Laboratories of Philadelphia.

revealed
she com-
al The
d easily
ht being
weight
nation
blind
ama-
sentially
4 mm
otherwise
erythro-
31 mg,
100 c.c.
olic rate
h blood,
per cent,
ull were
id French

normal, the sella turcica measured 8 by 11 mm and was regular in outline, the heart and lungs were normal

Treatment with ephedrine was tried, but brought only very slight improvement. Oral benzedrine sulphate medication, 10 mg three times daily, was begun after she left the hospital. At the end of two weeks' treatment she reported that "the first week I felt more like myself than I had for months. My whole system seemed to be alive. My head cleared and I did not have any of these peculiar spells (losing control of arms, legs, etc.) At the end of two weeks I stopped taking the tablets, and in a day or so the drowsiness returned and a slight tendency toward the peculiar spells [cataplexy]. I began taking the tablets again and that condition improved."

The treatment was omitted a second time. Two weeks later she wrote "my old spells are back upon me and seem to be just as bad. My hands are almost purple. My feet feel as if they were on ice, and across my forehead cold waves come and go and I just collapse, but pick myself right up and am all right until I have another. They certainly are very disagreeable, but not so very painful, unless I hit my head against a radiator as I have just done this evening."

She reported also that during the first period of medication the gastrointestinal symptoms recorded in the history (heartburn, gas and distress after meals) were present in an aggravated form, although she was not sure that the treatment was responsible for it. Later there was no evidence of gastrointestinal irritation by the drug. Since taking benzedrine she has slept much better and is no longer troubled unduly by unpleasant dreams.

Case 2 C E B, an American boy, aged 17, was admitted with the chief complaint of a constant tendency to fall asleep. This trouble began about seven years ago, was very pronounced during the subsequent three years, and then gradually subsided a little to reach its present level. There was no history of an immediately preceding illness.

He would fall asleep at any time, but especially while performing monotonous tasks (writing). Recently the attacks have lasted only a few minutes, but at first the duration was usually longer. Drowsiness has been more pronounced during warm weather and in a warm room. Occasionally he has had an attack while walking, and has lost his way. There have been no prodromal symptoms. He was easily aroused, but was made irritable thereby. There were also infrequent attacks of loss of muscular tone during which he did not lose consciousness but felt "as if my muscles won't hold me up." Such attacks have been usually elicited by excitement or laughter. They are much less frequent than they were formerly.

The family history was not relevant. The previous personal history revealed that he had mumps and pertussis before he was six years old. He was obese as a child. At age 10, at the onset of the present illness, he suddenly began to grow tall and is not obese at the present time. The present and highest weight is 155 pounds. There was slight tenderness in the right lower abdominal quadrant. The post-auricular lymph-nodes were palpable. The heart, lungs and ocular fundi were normal. The systolic blood pressure was 120 mm mercury, the diastolic was 60 mm.

The urine and blood count were normal. The non-protein nitrogen of the blood was 34 mg, uric acid 3.8 mg, sugar 87 mg, calcium 10.5 mg, phosphorus 4.1 mg, and cholesterol (whole blood) 130 mg per 100 cc. The blood phosphatase was 11.2 units. The Wassermann and Kahn tests were negative. Dextrose tolerance test: Blood sugar, fasting, 92 mg, one-half hour after dextrose, 111 mg, one hour, 105 mg, one and one-half hours, 105 mg, two hours, 93 mg. Cerebrospinal fluid: Cells numbered 2 per cu mm, the sugar was normal, globulin not increased, and colloidal gold and Wassermann tests were negative. The basal metabolic rate was minus 24 per cent. Roentgen-ray examination of the skull showed marked hyperostosis of the vault and retarded development of the sinuses, the sella turcica measured 6 by 9 mm and was regular in outline.

Treatment with ephedrine sulphate was tried without benefit. Benzedrine sulphate, 10 mg three times a day, was then given for two weeks with complete relief. The attacks of sleep recurred when the treatment was stopped. Resumption of the treatment was again followed by complete relief. The patient complained of slight anorexia for a few days at the beginning of each period of treatment. Ten mg twice a day were tried. This smaller amount of medication, taken over a period of several weeks, has been practically as efficient as the larger amount. Only an occasional slight drowsiness has been present after severe physical exertion, but he has not fallen asleep.

Case 3. A H., an American girl, aged 16, was admitted in September 1934, with the chief complaint of frequently falling asleep. In 1928, she had a febrile illness with pain in the jaw that was believed to have been mumps, although the diagnosis was not definitely established. Recovery was prompt. The tonsils were removed under ether anesthesia about a month later. About a week after that (at age 10), she fell asleep in school. Since then she has had frequent attacks of somnolence, sometimes five or six a day. They have lasted 10 to 20 minutes and usually have occurred in school, in church, in the theater, or during meals, rarely while she was walking. They were most frequent in the forenoon. An hour's sleep after the noon meal had a tendency to prevent attacks in the afternoon. Hearty laughter and, less often, anger or fear produced great weakness and a feeling of utter helplessness, as a result of which her head fell forward on the chest, and she was unable to raise or turn it. These cataplectic spells lasted five to 20 minutes. A nudge from a bystander quickly terminated them. She has had "horrible" dreams about snakes, beasts, etc., but they have been less troublesome at present. She has gradually gained weight since the onset of the present illness and now weighs 156 pounds.

Menarche occurred at age 11, one year after the onset of the narcolepsy. The periods have been normal. Thyroid medication, pushed to the point of making her nervous, has been used without benefit.

The family history was not contributory. There were no siblings. In addition to the questionable attack of mumps, she had measles at age five and chicken-pox at age eight.

Physical examination revealed moderate generalized obesity, slight hypertrichosis of the face, chest, abdomen and legs, and an oily skin. The labia minora were markedly hypertrophied. Otherwise the pelvic organs were normal. The ocular fundi, heart, lungs and abdomen were normal. The reflexes were hyperactive. The systolic blood pressure was 110 mm mercury, the diastolic 85 mm. The pulse rate was 72 per minute.

The urine contained a very slight trace to a trace of albumin, one to four blood discs per high power field, and increased indican, but was otherwise normal. The blood count was normal. The basal metabolic rate was minus 16 per cent and minus 22 per cent in two tests. Roentgen-ray examinations. Intravenous Graham test was negative, the skull was normal, the sella turcica measured 6 by 11 mm and was regular in outline, the heart and lungs were normal. The audiogram was normal. An electrocardiogram showed simple tachycardia (108), but was otherwise normal.

A diagnosis of narcolepsy and cataplexy, possibly on an encephalitic basis (mumps?), was made. Treatment with ephedrine sulphate was followed by moderate improvement. She was discharged with instructions to continue the treatment.

She reentered the hospital in April 1935 and reported that the medicine helped her for a few weeks after she left the hospital, but after the supply given her at the hospital was exhausted, she stopped taking it. Her physician then prescribed ovarian pills, apparently without effect. The attacks of somnolence were as frequent as before, and the cataplectic spells occurred about once a month and, as before, were induced by hearty laughter. She had no other complaints.

Having been at home for two weeks, during which time he had an irregular evening fever, he developed a sore throat. He was admitted to the Haines Memorial Hospital where he showed extensive ulceration of the soft palate and tonsillar pillars. The ulcerations were shallow, covered with a thin, white exudate and appeared like those seen in agranulocytic angina. The total white blood cell count was 2500 of which 35 per cent were polymorphonuclear leukocytes. Following nucleotide treatment the count rose to 3500, with 70 per cent polymorphonuclear leukocytes, and the throat rapidly cleared, but in spite of continued nucleotide treatment the count soon dropped once more to 2500 with 35 per cent polymorphonuclear leukocytes.

February 21, 1934, he was admitted to the Thorndike Memorial Laboratory with the complaint of soreness and stiffness in his joints and a drop in weight from his average of 137 pounds to 118 pounds, 15 pounds of this having been lost in the five preceding months.

Upon this admission, there was noted a pallor of the palms of the hands and nail beds. The firm, non-tender edge of the spleen was still felt two cm below the costal margin. The liver edge was not felt. There was slight enlargement of the inguinal lymph nodes. No abnormalities of the joints were noticed.

The blood findings were as follows: white blood cells 3,300, 55 per cent neutrophils, 4 per cent myelocytes, 6 per cent metamyelocytes, 28 per cent lymphocytes, 1 per cent monocytes, 6 per cent young neutrophils, red blood cells 2,700,000 and hemoglobin 62 per cent.

The basal metabolic rate, and the results of the phenolsulphophthalein kidney function test and of gastric analysis were found normal.

Sternal puncture, February 24, 1933, showed numerous normoblasts and nucleated red blood cells, some stem cells, only a few granulocytes and those mostly myelocytes, rare adult polymorphonuclear leukocytes, numerous megakaryocytes.

After eight days in the hospital, during which time there was no essential change, he was discharged to convalesce in Florida. He returned for a check-up, May 17, after having spent three months in the South, looking much improved. He had gained 21 pounds, had a deep tan, felt generally better but still had some pains in his joints though to a lesser extent.

Examination showed as the essential features: slight stiffness of the elbow joints and an easily palpable spleen two cm below the costal margin. The red blood cells had risen to 4,600,000, but the white count was only 3,200.

The patient got along quite well and was relatively free of arthritic symptoms until about August 10, 1934, at which time he began to have fever and chills, followed in a few days by a productive cough. On August 20, he was admitted with symptoms and signs of bronchopneumonia in the left upper lobe which soon spread to all lobes. At no time did the white count rise above 3,200 in spite of the fact that 40 c.c. of nucleotide per day were given beginning August 24. The patient died on August 28.

An autopsy, restricted to the chest and abdomen, was performed two hours post-mortem. The lymph nodes at the head of the pancreas and around the celiac axis were moderately enlarged, firm and uniformly light pinkish-yellow on cut section.

The visceral surfaces of the lungs were covered with a thin fresh layer of fibrin, and there were 400 c.c. of thin, straw-colored fluid in each pleural cavity. The left lung weighed 700 grams and the right 900 grams. All lobes were heavy, uniformly firm, very slightly crepitant and on cut section presented a uniform light gray, glistening surface, from which a small amount of seropurulent fluid could be scraped.

The spleen was moderately enlarged, weighing 260 grams. The capsule was smooth gray and glistening and the pulp dark red, firm, smooth, relatively dry. The cut surface yielded little on scraping. The trabeculae and Malpighian corpuscles were not very distinct.

The liver was moderately enlarged, weighing 2000 grams. The capsular and cut surfaces were smooth, firm, light brown and showed the lobules fairly distinctly.

In the distal three feet of the colon were many diverticula, averaging 5 mm in length and 4 mm in width. The mucosa of some of the diverticula was injected though not ulcerated.

The bone marrow in the middle of the femur and in the tibia consisted of fat, whereas in the upper end of the femur it was yellowish-red. Sternal and lumbar marrows were grayish-red and firm. There was moderate lipping of the bodies of the vertebrae and an increase in density of the bone.

Microscopic examination of all lobes of the lung showed an advanced organization with a diffuse infiltration consisting of a moderate number of polymorphonuclear leukocytes though there were almost as many plasma cells, lymphocytes and macrophages.

The Malpighian corpuscles of the spleen were not very large or distinct. The sinuses were inconspicuous. The pulp was highly cellular, consisting chiefly of red blood cells, lymphocytes and plasma cells. There was also a moderate number of macrophages, a few nucleated red blood cells and rare stem cells. A few macrophages had phagocytosed red blood cells. Polymorphonuclear leukocytes were scarce. The liver showed extensive hydropic degeneration. There was a slight increase in lymphocytes and plasma cells in the sinusoids and a few Russell's "fuchsin bodies."

In one adrenal was a focus of plasma cells, lymphocytes and macrophages.

Sections of the tracheal and mesenteric lymph nodes showed an obliteration of the normal architecture by the diffuse infiltration with plasma cells. There was a moderate number of macrophages and Russell's "fuchsin bodies" and a few stem cells and myelocytes irregularly scattered. Some of the macrophages had phagocytosed lymphocytes and red blood cells.

The lumbar marrow showed a moderate erythroblastic and lymphocytic hyperplasia. There were also many megakaryocytes, stem cells and plasma cells, myelocytes occurred in moderate numbers but adult polymorphonuclear leukocytic cells were quite scanty. The sternal and femoral marrows appeared similar though not quite as active.

The pathological diagnoses were bilateral organizing pneumonia, bilateral serofibrinous pleuritis, hepatomegaly, splenomegaly, enlargement of mesenteric and tracheal lymph nodes, hypertrophic arthritis, diverticulitis and diverticulosis of colon, hyperplasia of bone marrow with maturation arrest of the neutrophilic series (dysoremos neutrophilia).

Cultures of the heart's blood and spleen showed no growth while those of the lungs showed *Streptococcus viridans*.

ANALYSIS OF CASE REPORTS

As the clinical and pathological features of the above case conform rather closely to the nine previously reported cases they will all be discussed together.

All cases have been in individuals between 45 to 65 years, equally distributed between the sexes. The cases have been widely scattered geographically. The occurrence of a marked loss of weight, six to 65 pounds has been usual, with an average loss of about 40 pounds. Intermittent periods of moderate fever have been noted, rarely going above 101° F. The arthritis is invariably of a chronic type—only one case had less than two years' duration—showing repeated acute migratory exacerbations, characterized by pain, tenderness, limitation of motion, and less often by local heat and redness. The ankles, wrists or knees frequently are the first joints involved, but before this acute manifestation has subsided, the shoulders, elbows, interphalangeal and other joints are involved in rapid succession. After the acute phase, stiffness and slight limitation of motion not infrequently exist. Roentgenologically, the changes in the articular cartilages

and in the bones have not been marked Six cases showed changes suggestive of infectious arthritis, and three showed only minor indeterminate changes One case showed complete ankylosis of some of the joints

A firm, smooth, non-tender, persistently enlarged spleen has been noted in all cases, the inferior edge having been palpated at various points between the left costal margin and the level of the umbilicus The enlargement is usually quite definite and the spleen extended to the umbilicus in four cases Very little variation in size has been noted in the different cases upon repeated periodic examinations Four spleens have been studied pathologically, two as surgical specimens and two as necropsy specimens In three cases there was found dilatation of the sinuses, thickening of intersinusoidal spaces, enlarged Malpighian corpuscles with prominent germinal centers, and many plasma cells diffusely distributed In two cases there were a few phagocytosed red blood cells In the case of Craven and in that of Price and Schoenfeld there was noted an increase in eosinophiles In the case here reported the splenic corpuscles were not large and the sinuses inconspicuous There were many plasma cells, rare stem cells, occasional phagocytosed red blood cells, a few nucleated red blood cells, and relatively few polymorphonuclear leukocytes

In only two cases was the liver palpable clinically In the two cases operated upon the liver was found moderately enlarged, and the livers examined in the two necropsy cases weighed 2100 and 2000 grams, respectively Sections of liver in three cases examined showed nothing remarkable

In six cases there was noted pigmentation of the skin, confined chiefly to exposed surfaces

In five cases, there was more or less slight general lymph node enlargement Price and Schoenfeld noted "myeloid changes" in the material they examined In my case, sections of tracheal and mesenteric nodes showed an obliteration of the normal architecture by the diffuse infiltration with plasma cells, a few stem cells, rare myelocytes, and an occasional phagocytosed lymphocyte and red blood cell

All cases upon admission have shown a total white count varying from 800 to 4,200 with an average of about 2500 The admission differential showed the adult polymorphonuclear leukocytes varying from 14 to 79 per cent with an average of about 50 per cent, eosinophiles 1 to 12 per cent, 4 cases showing an eosinophilia at some time during the course of the disease, lymphocytes 14 to 86 per cent with an average of about 40 per cent There was no mention of young cells of the granulocytic series, except in Price and Schoenfeld's case, where 3 per cent of myelocytes were found on one occasion, and 2 per cent another time On one examination 20 per cent stabs were found In my case, myelocytes were frequently found, on one occasion to the extent of 9 per cent Young polymorphonuclear leukocytes were frequently found to exceed 30 per cent In most cases there was a great variation in the proportion of adult polymorphonuclear leukocytes from time to time

The red blood cell count varied from 3,000,000 to 4,800,000, and in all cases where many counts were performed, at some time in the course of the disease there was a drop below 3,500,000 The hemoglobin changes corresponded fairly closely with those of the red blood cells The morphological characteristics of

the red blood cells showed few changes. The platelets have occurred in normal numbers. The bleeding time and clotting time have been found essentially normal.

Bone marrow studies have been made only in the two necropsy cases. Price and Schoenfeld found the sternal marrow to show "hyperplasia of marrow for patient's age with few bone marrow giant cells. Active myelosis throughout." The lumbar marrow in my case showed a moderate number of megakaryocytes, plasma cells and stem cells. The most notable feature was a partial maturation arrest of the neutrophilic series (dysoremos neutrophilia), there being a moderate number of the younger cells, but adult polymorphonuclear leukocytes being rare. The sternal and femoral marrows were similar though less active.

Examination of the vertebral column in my case showed nothing more than the changes of hypertrophic arthritis. Price and Schoenfeld found the knee joint, in their case, to show active chronic inflammation of the periarticular tissue and a marked infiltration of the adjoining periosteum with lymphocytes and plasma cells.

Urobilin was found in the urine in four cases. In several cases the urine was not tested for this.

Two cases in which glucose tolerance tests were performed showed a decreased tolerance.

Bacteriological studies have been negative.

COMMENT

The etiology of this disease remains to be proved. No explanations beyond those suggested by Feltz have been advanced, namely, that there is one pathological process, caused by a toxin, which concomitantly affects the spleen, blood and joints, or that the arthritis is a process different from the remainder of the picture.

That there may be a blood dyscrasia is worthy of consideration, though further study is necessary to establish this as a fact. In Alessandrini's case what was thought to be a large spleen was found four years before the symptoms of arthritis began. In the other cases the relation is not known. Although the joint symptoms dated back for some time, the size and character of the spleens indicate that they had been enlarged for some time. In my case, the joint symptoms began only 10 days before admission, whereas the spleen was found two cm. below the costal margin, and in view of its pathological characteristics and the fact that it stayed at the same level, there is reason to believe that it may have been enlarged for some time.

The fact that soon after the splenectomy in Hanrahan and Miller's case there was a definite improvement of the arthritic symptoms, objectively as well as subjectively, within five weeks, and the fact that within four months the red and white counts were normal, suggest that the two processes are related and that a hematological basis may be the underlying cause. After splenectomy in Craven's case there was similar improvement, though not as marked. However, both from an etiological and therapeutic point of view it would be interesting to know the present status of these two patients, as not infrequently in other blood dyscrasias the improvement following splenectomy is only transitory.

In my case, a few stem cells and nucleated red blood cells were noted in the spleen, whereas adult neutrophils were relatively rare. In the lymph nodes were seen a few stem cells and myelocytes. The most significant hemopoietic changes were found in the bone marrow, which showed a hyperplasia of all series, and although many stem cells and myelocytes were seen, adult polymorphonuclear leukocytes appeared rather rare, there apparently being some inhibiting factor preventing many of these granular cells from reaching maturity. This condition of the marrow, though not as marked, is analogous to that seen in cases of agranulocytosis showing maturation arrest as described by Fitz-Hugh and Krumbhaar⁶ and later by Jackson and Parker.⁷ This inability of the bone marrow to generate many mature neutrophils was further manifested in my case at the time when with a severely ulcerated and sore throat, and later with a pneumonia, there was no increase in the polymorphonuclear leukocytes. There was a similar failure of response in Price and Schoenfeld's case during an attack of acute fibrinous pericarditis, and in all the other cases during the periods of acute exacerbation of the joint symptoms. Furthermore, if the bone marrow could generate polymorphonuclear neutrophils in a normal manner, the pneumonic lung in my case should have contained more polymorphonuclear leukocytes, whereas those present no more than equalled the number of lymphocytes and plasma cells. One would also expect the fibrinous pericarditis of Price and Schoenfeld's case to show a reaction consisting chiefly of polymorphonuclear leukocytes, but they describe the cellular reaction as consisting chiefly of lymphocytes, plasma cells and eosinophils. Additional evidence of a blood dyscrasia is the fact that with nucleotide treatment for several weeks there was no appreciable change in the white blood cell count in my case.

The number of adult polymorphonuclear leukocytes in the blood has sometimes been 20 per cent or less, and the bone marrow apparently attempts to compensate by sending out the younger forms into the peripheral blood.

With such lowering of so highly a potent barrier to infection, it is easy to see how noxious agents may gain a foothold, either through allergic mechanisms or by actual bacterial invasion, and produce the inflammatory changes noted in these cases. Just as in agranulocytosis there is a predilection for infections of the throat, so in these cases there is a predilection for the joints. Yet either may show manifestations elsewhere, such as acute fibrinous pericarditis, and pneumonia. One would expect to find associated inflammatory conditions more frequently if carefully sought for.

If one assumed allergy to play a role, it would be easy to explain the eosinophilia, the plasma cell and eosinophile infiltration in some of the organs and the rapid onset and disappearance of the acute arthritis without many sequelae. However, such an assumption is mere speculation.

Though agranulocytosis and Felty's syndrome seem to have many features in common, they are entirely separate entities. The former usually has a more sudden onset, is rapidly fatal if not treated, has a predilection for females, is very frequently associated with angina, and rarely has as high a white count. Of 103 cases analyzed by Jackson and Parker, 58 had white counts less than 1000 and only seven had a count of more than 2000. Moreover in agranulocytosis there is a more marked neutropenia, eosinophils are quite rare or absent, the spleen is rarely obviously enlarged and never greatly so, and the bone marrow shows but few if any adult neutrophils.

Still's⁸ disease is similar in that there is a chronic arthritis, splenomegaly, enlargement of the lymph nodes, fever, emaciation, occasional eosinophilia, secondary anemia and rarely subcutaneous nodules. It is different in that it occurs in children, usually has a leukocytosis rather than marked granulopenia and neutropenia, and is characterized by a more crippling form of arthritis.

Many of the features of these cases are similar to those of other forms of chronic rheumatoid arthritis. Of 250 cases of chronic arthritis studied by Eaton⁹ there were only three cases with a normal blood picture. The hemoglobin was below 75 per cent in 68.8 per cent of the cases and below 60 per cent in 15.2 per cent, the red blood cell count was below 4,000,000 in 10.4 per cent, the white blood cell count below 6000 in 22 per cent, the polymorphonuclear leukocytes under 60 per cent in 43.2 per cent, the lymphocytes over 35 per cent in 47.2 per cent. A marked shift to the left occurred in 37.2 per cent, with 2 to 15 per cent juvenile polymorphonuclear leukocytes in 44 per cent, and 5 per cent or more eosinophiles in 9.2 per cent. Pemberton and McRae each analyzed a large series of cases and, though differing to some degree in the figures, found essentially the same general changes. Slight enlargement of the spleen and eosinophilia associated with chronic arthritis have been frequently described. However, in no case have I been able to find such persistently marked leukopenia or granulopenia (adult polymorphonuclear leukocytes sometimes being less than 10 per cent). Nor has there been such failure of response of the white count in the presence of swollen, hot, painful joints or such acute infections as fibrous pericarditis (Price and Schoenfeld), angina and pneumonia.

SUMMARY

1 The cases of Felty's syndrome which have been reported have shown it to be a disease of middle-aged individuals characterized by migratory, polycyclic chronic arthritis, splenomegaly, marked leukopenia, marked granulopenia, distinct loss in weight, slight secondary anemia and intermittent fever. Less often there have been noted enlargement of lymph nodes, pigmentation of the skin, urobilinuria, enlargement of the liver and eosinophilia. Two cases have been treated with some improvement by splenectomy.

2 A case of this disease with autopsy is reported.

3 An attempt has been made to explain the primary disturbance as a blood dyscrasia in which there is an arrest in the maturation of the polymorphonuclear leukocytes (dysoremos neutrophilia).

REFERENCES

- 1 FELTY, A. R. Chronic arthritis in the adult, associated with splenomegaly and leukopenia, *Bull. Johns Hopkins Hosp.*, 1924, **xxv**, 16.
- 2 HANRAHAN, E. M., and MILLER, S. R. Effect of splenectomy in Felty's syndrome, *Jr. Am. Med. Assoc.*, 1932, **xcix**, 1247.
- 3 CRAWFORD, E. B. Splenectomy in chronic arthritis, associated with splenomegaly and leukopenia (Felty's syndrome), *Jr. Am. Med. Assoc.*, 1934, **cii**, 823.
- 4 ALESSANDRINI, P. Felty's syndrome, *Minerva Med.*, 1934, **i**, 310.
- 5 PRICE, A. E., and SCHOENFELD, J. B. Felty's syndrome, report of a case with complete postmortem findings, *Ann. Int. Med.*, 1934, **vii**, 1230.

- 6 FITZ-HUGH, T, JR, and KRUMBHAR, E B Myeloid cell hyperplasia of the bone marrow in agranulocytic angina, *Am Jr Med Sci*, 1932, *clxxxiii* 104
- 7 JACKSON, H, JR, and PARKER, F, JR Agranulocytosis, its etiology and treatment, *N E Jr Med*, 1934, *ccxii*, 137
- 8 STILL, G T On a form of chronic joint disease in children, *Med-Chir Soc Trans*, London, 1897, *lxxx*, 47
- 9 EATON, E R Chronic arthritis, a report based on the blood cell count in 250 cases, *Jr Am Inst Homeop*, 1932, *xxxv*, 125

NEUROCIRCULATORY ASTHENIA REPORT OF A CASE TREATED BY ADRENAL DENERVATION *

By JOHN P ANDERSON, M D, F A C P, *Cleveland, Ohio*

THE term, neurocirculatory asthenia, is used to represent a syndrome characterized by a sense of fatigue, palpitation, precordial pain, and a tendency to giddiness. The symptom complex it presents is almost as definite as that of angina. It has been called by various other names, for example, irritable heart, effort syndrome, and disordered action of the heart, but none is quite so descriptive as neurocirculatory asthenia.

Persons afflicted with this condition are usually thin and asthenic in stature and appearance. They have quick, nervous temperaments and are intelligent. They have a marked degree of initiative but usually lack the physical stamina to carry on sustained activity without suffering undue fatigue. Whether this is essential to the syndrome or incidental is unknown. It would appear that they have been unable to train their involuntary nervous systems and still react to fear, joy, sorrow and other emotions as adolescents, but whether this is due to lack of effort on their part or to a hypersensitive involuntary nervous system is uncertain.

Dr Crile has suggested that the condition of neurocirculatory asthenia is caused by excessive adrenal activity which produces increased drive on the whole involuntary nervous system. On this basis he has advocated adrenal denervation, and this report illustrates the beneficial effects of the operation in controlling the circulatory symptoms in a patient with neurocirculatory asthenia.

CASE REPORT

A single girl, aged 21 years who was employed as a secretary, first consulted Dr Crile in 1921 for nervousness and enlargement of the neck. Her birth had been premature (at seven months) and difficulties had been encountered in maintaining her nutrition. She had always been considered as a delicate child. She had had diphtheria in childhood, and following this a tonsillectomy had been performed. The menses were regular and normal with no pain.

She stated that her neck had been slightly enlarged and that she had been a little nervous for several years, but that during the last year these symptoms had progressed. She also suffered from insomnia. She noticed palpitation and slight dyspnea with effort and also had difficulty in swallowing when she was nervous, she said she felt as if she had a lump in her throat. There had been no loss of weight. Her appetite was good and she had had few digestive upsets. The bowels were regular,

* Received for publication January 2, 1935

and there was no bladder frequency or nocturia. She had very few colds, but complained that she tired very easily.

On examination, she was 5 feet, 7 inches tall and weighed 130 pounds. There was a slight symmetrical thyroid enlargement with increased pulsation of the superior thyroid vessels. The heart was not enlarged. The pulse rate was 120. The diagnosis was mild hyperthyroidism, and an operation was performed at which 40 grams of thyroid tissue were removed. This the pathologist reported as colloid goiter with no hyperplasia.

In 1923, the patient reported that she still fatigued easily, was less nervous, but still had palpitation. Her weight had not changed. It was thought that she probably had recurrent hyperthyroidism and sedatives were prescribed.

From 1923 to 1930 she worked steadily as a stenographer and secretary for a busy executive. She was annoyed by palpitation and fatigued easily. She was full of ambition but lacked the physical ability to accomplish what she wished without undue fatigue, and she had to force herself to get through her work.

I first saw her in June 1930, when she consulted me for an examination of her heart condition. This was prompted by the fact that she had twice been refused life insurance and had been unable to obtain permission to swim in a Y W C A pool, because of a rapid heart rate. At that time, she still weighed 130 pounds. The temperature was 98.6° F, the pulse rate 126, and the blood pressure 138 systolic, 70 diastolic. She had no exophthalmos and no lid lag, and there was no palpable thyroid tissue, but she displayed some digital tremor and seemed nervous. Her extremities were clammy. The heart was not enlarged. The sounds were clear and without any murmurs. There were no signs of congestive failure in the lungs, liver or extremities and no cyanosis of the extremities.

My first impression was that she had recurrent hyperthyroidism but the basal metabolic rate was —11 per cent, which immediately raised the question of neuro-circulatory asthenia. Lugol's solution was administered daily for one month. The patient was still nervous and irritable and the pulse rate varied between 100 and 120. There was still some digital tremor. The Lugol's solution was continued for another month. She then had no digital tremor, the basal metabolic rate was —7 per cent and the pulse rate 88.

In October 1930, she had been working hard and was excessively stimulated. She was troubled with insomnia, her hands were cold and clammy, the pulse rate was 150 and the blood pressure 130 systolic, 70 diastolic. The administration of Lugol's solution was renewed daily, and a month later the pulse varied from 96 to 108, and she had a marked sinus arrhythmia. An electrocardiogram showed nothing abnormal aside from the sinus arrhythmia. The Lugol's solution was discontinued and a month later the pulse was 130.

Her condition remained unchanged for four months until April 1931. At that time she was working very hard and felt nervous, and her ankles were swollen. Digitalis was prescribed (1 gram three times daily). This induced nausea on the eighth day but the edema had disappeared. The pulse rate was 100. The digitalis was continued, but even very small doses induced nausea and she refused to take any more. In July 1931, ammonium chloride and salyrgan were started and were continued on an average of once a week for six weeks. The pulse rate averaged 130 each time she was observed, but the salyrgan controlled the edema of the legs. There were never any pulmonary congestive râles or tenderness of the liver.

In November 1931, she made a trip to California and had no trouble on the way. Her nervousness subsided while she was away. In December 1931, her ankles were still slightly swollen and her extremities were cold, clammy and mottled.

In July 1932, her chief complaint was easy fatigability and aches at the back of the neck. She said that she had noticed the cold a great deal during the past winter and always required about twice as many bed clothes as other persons. She had

recognized no edema during the last year. Her heart continued to thump at the slightest provocation and her extremities continued to sweat easily. She had used no medicine.

At examination on July 16, 1932, that is, two years after my first examination, the temperature was 99°, the pulse rate 126 and the blood pressure 130 systolic, 80 diastolic. The hands were warm and clammy. She displayed no cyanosis, no thyroid or lymph glandular enlargement, and the lungs were clear. The heart borders were 3 and 10.5 cm, the sounds were regular with a systolic murmur at the apex. The remainder of the examination, including a blood count and urinalysis, was normal. An electrocardiogram showed normal rhythm and conduction with inverted T₃. Vagal pressure, eye ball pressure, or bending over and compressing the abdomen caused no appreciable change in the pulse rate, but lying down reduced it from 126 to 108.

She received Lugol's solution (8 minims twice daily) for two weeks, but this produced no change in her condition. The pulse rate when standing was 120, when lying down, 72 to 88, after touching toes 15 times, 132, after lying down it reached 72 with marked sinus variation. Deep inspiration caused marked slowing of the pulse with sinus arrhythmia, whereas before she had taken the Lugol's solution, this had produced no change.

After consultation with Dr. Crile, she was advised to have an adrenal denervation and she entered the Cleveland Clinic Hospital in September 1932, with symptoms of tremor, cold hands, palpitation, tachycardia (pulse rate 130), nervous excitability and fatigability, and flushing of the neck and chest. The basal metabolic rate was -8 per cent.

Dr. Crile performed a left adrenal denervation on September 28, 1932, and right denervation on October 11, 1932. She was in the hospital 23 days. On discharge, her hands were warm and dry and she had no tremor. She was sleeping well and could relax easily without any sense of inward nervousness and had no palpitation or precordial distress. The pulse rate was 80. One month later she was feeling well and the pulse rate was 74. The extremities were dry and warm, she had no palpitation and the flushing of the neck had disappeared.

For one year she lost an average of two pounds each month. In February 1933, her menses became irregular. One period interval would be four weeks and the next two weeks. Examination showed that the right ovary was about twice the normal size and the presence of a retention cyst was suspected. Six injections of antuitrin S were administered and the menses became regular.

During the hot weather that summer there was some aching under the left scapula but the patient had no palpitation or edema. The pulse rate remained between 72 and 78. The menses became irregular again in August 1933. Antuitrin S seemed to help regulate them, but when larger and larger doses were required, its use was abandoned.

The patient then had irregular menses with periods of amenorrhea for two to four months. In September 1933, one year after the operations, her weight had fallen from 129 to 100 pounds, and she then complained of marked urinary frequency and urgency. The urine was examined and showed no pus or casts but 1+ albumin, the specific gravity was 1.033. Another specimen was collected in the early morning and showed no albumin which indicated that the albuminuria might be postural. A 24 hour output was then recorded and it was over 4 liters, of which the night specimen was 1125 cc.

Several doses of pitressin were given hypodermically and the 24 hour urinary output was recorded afterwards. These were 3000, 2000 and 1500 cc respectively. There was no further loss of weight after these injections, and three months later she had gained five pounds. Although the pulse rate and blood pressure did not change, the injections of pituitary extract always caused a little shock and nausea and the

patient preferred not to continue them. Whole pituitary substance was given in doses of 5 grains daily, but caused very little effect, so it was discarded.

To date, September 1934, her condition continues about the same. She has gained no more weight. There is still an excessive urinary flow with much urgency at times. The menstrual periods are irregular. An osteoma developed along the crest of the left ilium which was a little tender to pressure. The blood calcium is 10.78 mg per cent. The heart has remained entirely stable. The pulse rate has never been above 90 since the denervation of the adrenal glands, and the rate is usually 72 to 78. The systolic murmur at the apex is now barely audible. There has never been any recurrence of the sense of palpitation, flushing, inward nervousness or cold extremities, and there has been no undue fatigability in spite of the loss of weight. The patient herself is most enthusiastic about the results of the operation.

COMMENT

In my experience, neurocirculatory asthenia has been rather difficult to control with medical measures. Digitalis has little or no effect in slowing the heart rate and no effect on the other symptoms. Sedatives such as bromides and barbiturates have little effect, and drugs which act on the sympathetic nervous system, such as quinine and ergotin and ergotamine, have been of but questionable value. In fact, the only thing that has really helped has been about one or two years of intensive rest and convalescent treatment, and that is a form of therapy that is seldom practicable. The fact that a thyroidectomy was performed on this patient in 1921 and failed to cure her symptoms indicates once again that the symptoms of neurocirculatory asthenia are not relieved by thyroidectomy.

It is very gratifying in this case to find a complete cure of all the symptoms of neurocirculatory asthenia by the adrenal denervation, although there is evidence of a disturbance of the pituitary gland following the operation. The fact that there was an increased urinary output with a negative water balance which appeared after the operation along with irregular menses and later amenorrhea when both of these factors had been very stable prior to the operation is presumptive evidence, at least, of some hypofunction of both the anterior and posterior lobes of the pituitary gland.

But despite these complications, the patient's condition has been very much better generally, and the abnormality of the circulation has been entirely controlled since the operation.

PAROXYSMAL VENTRICULAR TACHYCARDIA, REPORT OF A CASE ILLUSTRATING ALL THE ACCEPTED DIAGNOSTIC CRITERIA^{*}

By AARON E. PARSONNET, M.D., C.M., F.A.C.P., *Newark, New Jersey*

ALTHOUGH there is a growing tendency among recent authors to minimize the rarity of paroxysmal ventricular tachycardia, nevertheless, when all the accepted criteria warranting such a diagnosis are made requisite, this type of abnormal cardiac rhythm looms rarer than ever.

The literature, starting with the work of Lewis,¹ has been materially enriched by contributions devoted to the study of paroxysmal tachycardias, some of which

^{*} Received for publication September 10, 1935.

are unquestionably of the ventricular type. However, after careful scrutiny of the available material, a large percentage of the reported cases falls by the wayside as either unproved, doubtful as to point of origin, or totally worthless for statistical data because of lack of electrocardiographic corroboration. In two exhaustive studies made by Gilchrist² and Strauss³ the former accepts practi-

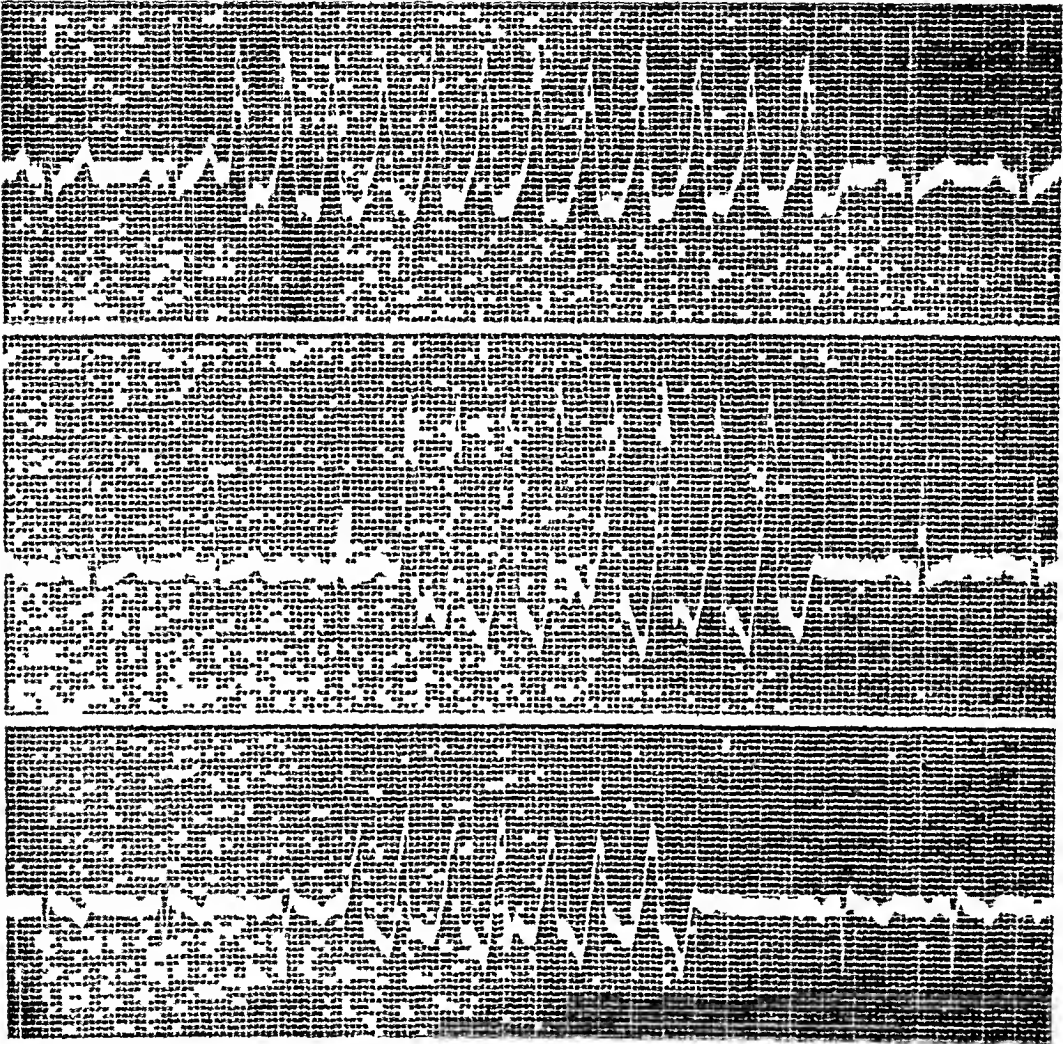


FIG 1 Tracing taken on May 10, 1932, showing the typical paroxysms of ventricular tachycardia. The variations in the length of the interventricular intervals may be distinctly observed.

cally all reported cases as true ventricular paroxysms while the latter, on the other hand, disposes of the majority of the 65 instances recorded up to 1930, as distinctly doubtful. There is a definite reason for such marked diversity of opinion among careful investigators: electrocardiographic methods of examination are still quite recent and poor tracings and standardizations were the rule up to but a very few years ago. With the practically perfect modern instruments and, of still greater importance, the improved technic and resultant rapid handling

of suspected patients, a paroxysm will rarely escape the observer and a good permanent record will be secured

The criteria warranting the diagnosis of paroxysmal ventricular tachycardia as outlined by Robinson and Herrmann,⁴ must be fully met and are as follows

1 The electrocardiographic tracings must definitely establish the fact that the cardiac impulses responsible for the rapid ventricular rate are of distinct ventricular origin

2 The ventricular complexes must be both preceded and followed by auricular complexes of slower rate

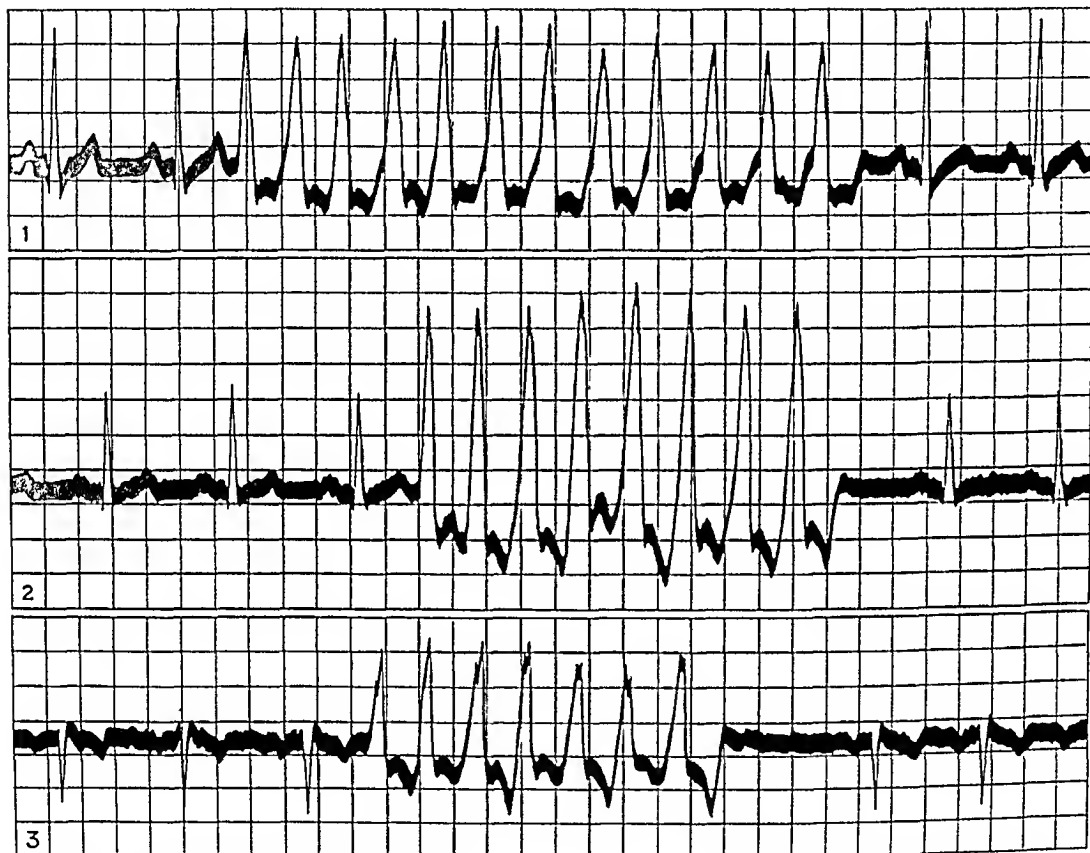


FIG 2 Schematic representation of the above tracing to more clearly note the characteristics of the paroxysms

3 The ventricular complexes must be abnormal in form and, should there be any isolated extrasystoles preceding or following the paroxysm, these must resemble in type the ones seen during the attack of tachycardia

In this connection, Robinson and Herrmann⁴ point out that the abnormal ventricular complexes alone cannot serve as proof of ventricular origin, for their bizarre form may be produced by intraventricular conduction disturbances. If, however, at the termination of the paroxysm no such disturbed conduction is exhibited, the unusual form of the complexes will serve further to substantiate their ventricular origin. Robinson⁴ also brought out the fact that, when the cardiac rate is very fast, conduction disturbances may often be overlooked. The

diagnosis of paroxysmal ventricular tachycardia can be made still more certain when, as Strong and Levine⁶ pointed out the rapid succession of ventricular complexes discloses a slight but nevertheless a definite irregularity of time spacing not met with in any of the other forms of paroxysmal tachycardia

It would be useless repetition and distinctly burdensome to give a detailed review of the literature, this has been very ably done by Strauss³ It is interest-

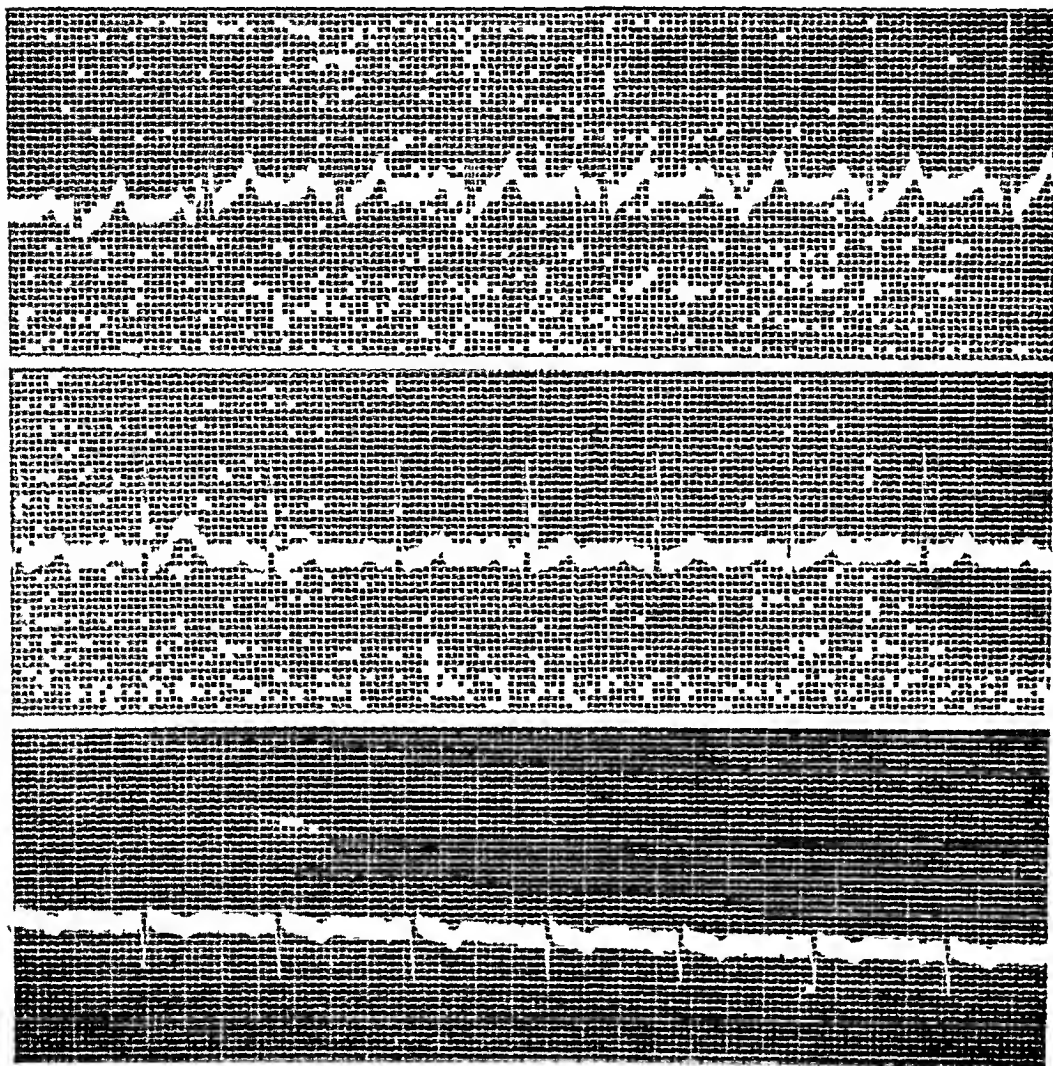


FIG 3 Electrocardiogram obtained before the onset of the paroxysm

ing to note, however, that as late as 1921, the entire number of published cases comprised 16, of which only six could be considered authentic. The writer's experience has been similar for, although over 90 cases were carefully examined in the available literature, the data in a large percentage were found unconvincing

It is not amiss, therefore, to present the following case of paroxysmal ventricular tachycardia exhibiting all the essential electrocardiographic features of this still rather rare arrhythmia

CASE REPORT

History F. C., male, aged 63, a native of the United States, receiving clerk by occupation, was seen in consultation on May 10, 1932. His chief complaints at the time were dyspnea upon exertion, precordial discomfort and occasional attacks of palpitation. His family history was unimportant, his parents having died of old age and one brother and two sisters during infancy. His previous history was un-

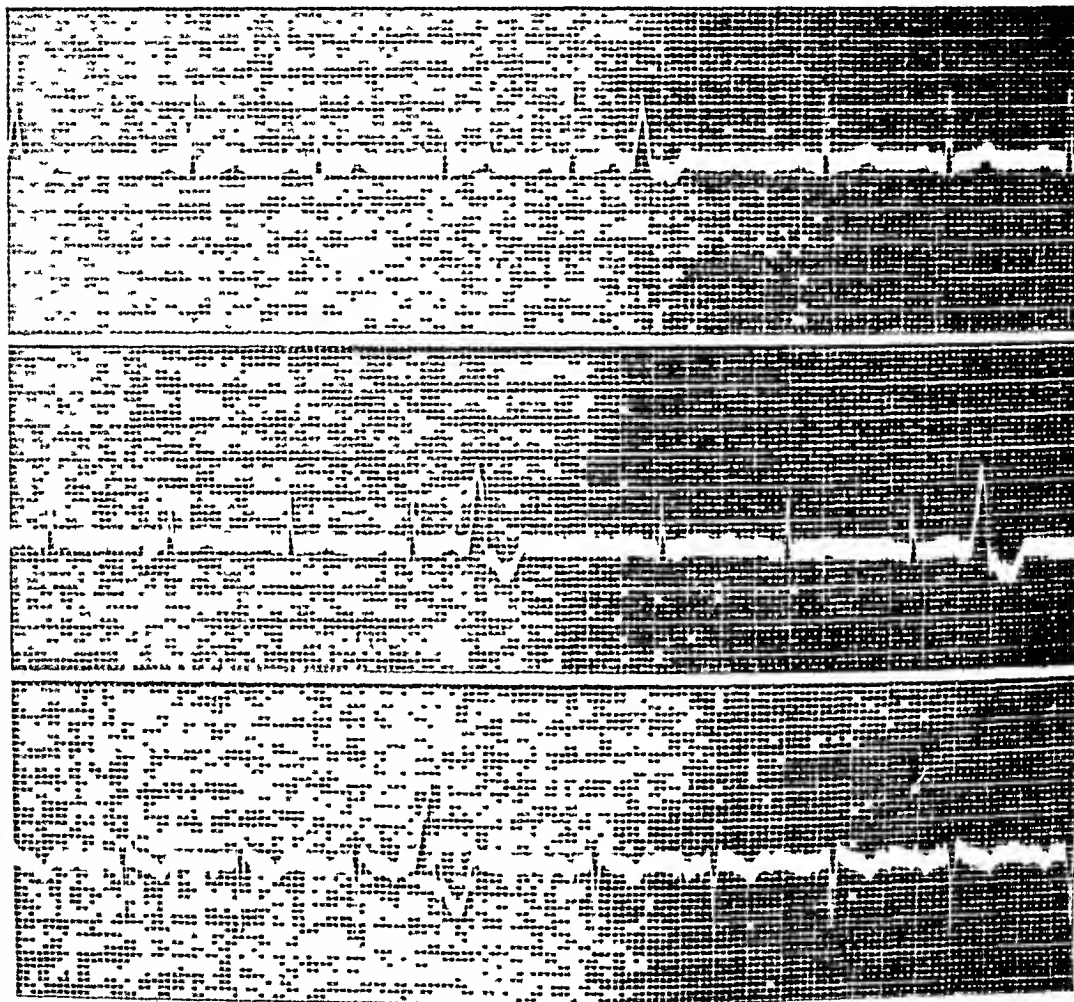


FIG 4 Electrocardiogram taken after the paroxysm subsided. Note the isolated extra-systoles in each lead and compare their form with those in figure 5.

eventful, except for the usual diseases of childhood and a minor surgical operation for ischiorectal abscess at twenty-five. He had been married 35 years, and had six children all living and well. His wife always enjoyed good health and gave no history of miscarriages or stillbirths. He was always temperate in his habits, using no tobacco or alcohol and drinking tea and coffee moderately. His exercise consisted chiefly in walking to and from work. He always enjoyed a good appetite, was a hearty eater, but habitually was a very poor sleeper.

Present Illness Although dyspnea and palpitation were symptoms familiar to him for the last year or two, he was quite sure that these were very much aggravated

since the beginning of April 1931, when in the course of his work he met with an accident. A heavy bale of wrapping paper struck him, knocking him down and fracturing his right clavicle and arm, he also received a crushing blow over the left chest, but no ribs were broken. Following this occurrence he became very short of breath even upon the slightest exertion, and the dyspnea would invariably be accom-



FIG 5 Redrawn section of the electrocardiogram (figure 1), isolating one ventricular complex from each lead and comparing it with the corresponding ectopic beat in figure 4. Note the striking structural similarity.

panied by marked precordial pain and palpitation. At times, while walking, he would stop short, being conscious of a sudden beginning and termination of rapid heart action.

Physical Examination The patient was 5 feet, 7 inches tall, and weighed 170 pounds. He appeared chronically ill, very dyspneic, and slow and deliberate in his movements. His skin was free from eruptions, dry, and had a leathery feel; his lips and nail-beds were moderately cyanosed. Oral examination showed moderate dental sepsis, with many teeth missing; the tongue was thickly coated. The naso-

pharynx was normal. The sinuses transilluminated well and the larynx was freely movable. There was no thyroid enlargement. The eyes reacted to light and to accommodation; the pupils were regular, both palpebral fissures equal. The conjunctivae were clear. A well-marked arcus senilis was present. The ophthalmoscopic examination revealed increased tortuosity of the retinal vessels.

The chest was well formed and disclosed no abnormal prominences or depressions, but scattered moist rales were heard posteriorly in both bases.

The heart was enormously enlarged to percussion in all its diameters and the aorta markedly widened. The heart sounds were muffled and toneless and the regular rhythm was frequently interrupted by extrasystoles, isolated and in showers. These were detected with difficulty at the radial artery. There was a marked pulse deficit. Under a moderate spirometric exercise test the patient became cyanotic and very dyspneic, showing a very poor myocardial reserve. An occasional systolic blow was heard at the apex which was also elicited over the aortic area. Repeated blood pressure readings averaged 140 systolic and 40 diastolic.

The abdomen was prominent, no masses and no ascites were noted. The liver was enlarged and tender to pressure, the lower margin extending four fingers below the costal margin. The spleen was not palpable.

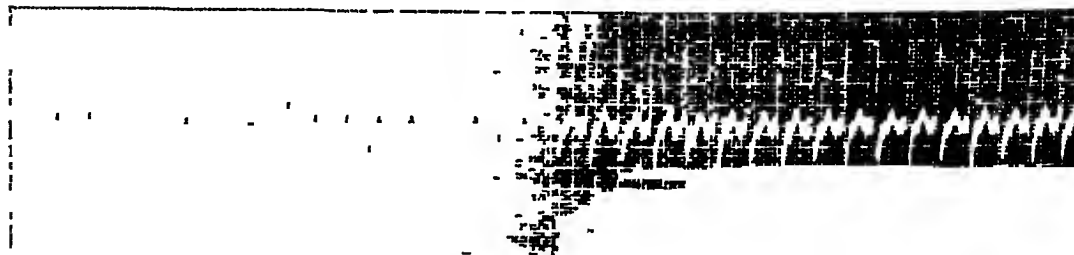


FIG. 6. A tracing of a typical proximal auricular tachycardia inserted for comparison. Note the practically clock-like regularity of the interventricular time intervals here as compared with the variations in the interventricular intervals as seen in figure 1.

The genito-urinary tract, with the exception of a moderately enlarged prostate, disclosed no abnormalities.

Fluoroscopic examination revealed a markedly enlarged cardiac shadow, aortic in configuration, a very much widened aorta and an accentuated aortic knob. The transverse diameter of the chest measured 29.7 cm, with a maximum transverse cardiac diameter of 18.8 cm. The lung fields were clear. The diaphragmatic excursions were limited.

Laboratory Data. The urine showed a 1 plus albumin test, a few small granular casts and an occasional pus cell; many cylindroids were noted. The blood count showed a hemoglobin of 82 per cent with 4,400,000 red blood cells, and 9,600 white blood cells. The differential count showed 59 polymorphonuclears, 37 lymphocytes and 4 eosinophiles. The blood chemical tests showed a urea nitrogen of 16.8, creatinine 1.5, and sugar, 95 mg per hundred cubic centimeters. The Wassermann and Kahn tests were negative.

The electrocardiograms taken on May 10, 1932 (figures 1 and 2) showed the following: There were no gross errors of conduction. The P-R intervals were 0.20 sec, the QRS complexes were upright and of high voltage in Leads I and II, and inverted in Lead III, showing a left axial rotation. The T-waves were dominantly upright in Leads I and II, and inverted in Lead III. They exhibited a low take-off in Lead I. The P-waves were upright in Leads I and II, and inverted in Lead III. The dominant rhythm is interrupted in every lead by showers of ventricular extrasystoles reaching a rate of 210 beats per minute. All the ectopic beats originate from

a single ventricular focus of irritability (figures 4 and 5) The auriculoventricular rate before the onset of the paroxysm is 90 beats per minute (Figure 3)

The patient is now 66 years old and has had several severe attacks of coronary occlusion, the paroxysms of ventricular tachycardia still continue at irregular intervals

SUMMARY

A case of undoubted paroxysmal ventricular tachycardia is reported in which all the essential criteria warranting such a diagnosis are exhibited An exhaustive review of most of the available literature established the rarity of cases of this condition properly authenticated by satisfactory electrocardiographic proof Such proof, however, is here presented as unmistakable evidence for the above diagnosis

BIBLIOGRAPHY

- 1 LEWIS, T Paroxysmal tachycardia, *Heart*, 1909-1910, 1, 43
- 2 GILCHRIST, A R Paroxysmal ventricular tachycardia, *Am Heart Jr*, 1926, 1, 546
- 3 STRAUSS, M B Paroxysmal ventricular tachycardia, *Am Jr Med Sci*, 1930, clxxx, 337
- 4 ROBINSON, G C, and HERRMANN, G R Paroxysmal tachycardia of ventricular origin and its relation to coronary occlusion, *Heart*, 1921, viii, 59
- 5 ROBINSON, G C The relation of changes in the form of the ventricular complex of the electrocardiogram to functional changes in the heart, *Arch Int Med*, 1916, lviii, 830
- 6 STRONG, G F, and LEVINE, S A Irregularity of ventricular rate in paroxysmal ventricular tachycardia, *Heart*, 1923, v, 125

EDITORIALS

THE DETROIT AND ANN ARBOR SESSIONS

THE return of the College, after ten years, to the city of Detroit gave to many of the older members an opportunity both to evaluate the progress of the College in this period of time and to appreciate the many alterations and advances in the medical institutions of Detroit and Ann Arbor. Changes have taken place, a normal healthy development has occurred. The College brought to this meeting a larger group of men better able to enjoy the richer intellectual fare provided for them.

In the minds of all was the memory of the man to whom the College owes so much, Dr. Charles G. Jennings. Both in the development of the policies of the general body of the College and in arousing the interest of the medical men of Michigan in the value of the College, Dr. Jennings played an important part. He it was who transmitted to the Regents the invitations to the College from the Medical Schools, the Hospitals and the Medical Societies of Detroit and Ann Arbor, to hold the Sessions of 1936 in Michigan. The acceptance was based in no small part upon his agreement to act as General Chairman. The success of this meeting constitutes a tribute to him since much of the labor was his and since those who took up the burden when he dropped it were his friends and carried out the work in the spirit of his wishes.

Perhaps at no meeting has there been more satisfaction among the Fellows both with the high quality of the General Sessions and with the interest and variety of the program of clinical meetings. The gratitude of the College is due to all who took part in the laborious task of arranging this highly successful meeting.

PNEUMOCOCCUS TYPE III PNEUMONIA

THE differentiation of the pneumococci into biological types led naturally to the hope that more intensive study of the clinical aspects of lobar pneumonia would disclose characteristic features which would be distinctive for the pneumonia caused by each type of the pneumococcus. This hope has as yet been only partially fulfilled, but a recent study by Cecil, Plummer and McCall¹ of 500 cases of Type III pneumonia adds further data in confirmation of earlier work that established important clinical facts bearing on infection with this organism.

The analysis of the incidence of Type III infections has shown again that though in the total of all pneumococcus pneumonias only about one in eight is due to Type III infection, in pneumonias occurring after 60 years of age Type III pneumococci are the commonest etiologic agent. In this age group the authors found in their recent study 32.8 per cent of Type III.

¹ CECIL, R. L., PLUMMER, N., and MCCALL, M. *Pneumococcus Type III pneumonia*, *Am. Jr. Med. Sci.*, 1936, vol. 305-319.

infections In all cases over 50 years the incidence of Type III infections was 24.2 per cent, while in cases under 50 years it was only 9.4 per cent Since these figures accord well with those found in earlier series published by Cecil, Baldwin and Larsen² and by Blake³ it may be considered clearly demonstrated that Type III pneumonia is a relatively rare variety before 50 but becomes the commonest type in the elderly

The death rate in the 500 cases of Type III pneumonia analyzed was 42.2 per cent This is in very close agreement with the figures derived from other large series It seems, however, that this high death rate is not necessarily due entirely to the excessive virulence of the organism The death rate of all types of pneumonia increases with each decade after maturity Since Type III pneumonias are common among the aged, it is evident that a part of the high death rate may be due to the lessened resistance of those attacked In the Bellevue series Cecil, Plummer and McCall have found that the death rate for Type III cases under 40 is not significantly higher than that of Type I or Type II Approximately 40 per cent of all the Type III cases, however, were over 50 years of age, whereas only 18.4 per cent of the Type I cases were over 50 and only 31.7 per cent of the Type II cases That the age incidence is, therefore, a factor in determining a part of the high mortality of Type III infections seems clear

Another factor apparently is the tendency of Type III infections to attack those already debilitated by chronic disease In the present series the incidence of systemic diseases, especially alcoholism and degenerative cardiovascular diseases, was 49.6 per cent Blake found that even in the earlier age periods this same tendency could be observed Comparable figures given for series of Type I and Type II cases show that systemic disease occurred in only 20.4 and 33 per cent respectively of these infections

These considerations of the factors bearing on the virulence of the Type III pneumococcus seem of particular interest The fact that this organism, unlike the Type I and II pneumococci, is not infrequently found as an apparently harmless saprophyte in the mouths of healthy individuals has always raised the question as to what determined its behavior in the cases in which it causes a highly fatal infection

To this fundamental question no answer has been given, but when a more complete understanding is attained the explanation must include the behavior of this organism in relation to age and to chronic disease

² CECIL, R. L., BALDWIN, H. S., and LARSEN, N. P. Lobar pneumonia: a clinical and bacteriologic study of two thousand typed cases, *Arch. Int. Med.*, 1927, xl, 253-281

³ BLAKE, F. G. Observation on pneumococcus Type III pneumonia, *Ann. Int. Med.*, 1931, v, 673-686

BOOK REVIEWS

Laboratory Methods of the United States Army Edited by MAJOR JAMES S SIMMONS and MAJOR CLYDE J GINTZKOW (Associate editor) Fourth edition Lea and Febiger, Philadelphia 1935 1091 pages Price, \$6.50

This new edition of the Army Manual has been largely rewritten and considerably extended in scope. Twenty contributors are listed, chiefly members of the Medical Corps on the staff of the U. S. Army Medical School.

The book is primarily a laboratory manual. It covers in a severely practical way the usual field of medical bacteriology, serology, protozoology and clinical pathology, including quantitative chemical analyses of the blood and urine. There are also brief sections on mycology, on the helminths and on the more important mosquitoes and other arthropod vectors, with tables and keys to facilitate identification. The individual parasites are not described, however. In addition there are sections on the filtrable viruses, chemical and bacteriological examination of water, milk, foods and beverages, toxicological procedures, autopsy technique and preparation of tissue sections, special methods applicable to veterinary medicine, and statistical methods.

The technique of the various laboratory examinations is given in detail, and the underlying principles are clearly explained, so that the procedures can be followed by technicians with limited experience. As a rule the authors have selected a single analytical method for each determination with occasionally an alternative procedure. In most instances the selections seem wisely made. Relatively less attention is paid to the clinical significance of the tests except in a few instances. Thus, tests of liver function and of kidney function are discussed at considerable length.

In general the subjects are adequately covered, and the work is reasonably well balanced. As is usually the case in books which are the product of a number of contributors, some subjects seem unduly stressed at the expense of others. The reviewer regrets, for example, that only 18 pages were allotted to hematology, less than half the space devoted to tests of liver function. He was also unable to find a description of the glucose tolerance test.

On the whole the book is well written and accurate and contains a great deal of carefully selected, useful information. It should be of great assistance to those who are engaged in the actual performance of these procedures. P. W. C.

The Practitioner's Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M. A. (Yale), M. D., F. A. C. P. David P. Smith, Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital. Volume IX *Neurology and Psychiatry* Associate Editors, JAMES C. FOX, JR., B. A., M. D., Associate Professor of Neurology, Yale University School of Medicine, and CLEMENTS C. FRY, B. S., M. D., Associate Professor of Psychiatry and Mental Hygiene, Yale University School of Medicine. xviii + 1234 pages, 193 illustrations. D. Appleton-Century Company, Inc., New York. 1936. Price, \$10.00 a volume.

In the preface to this ninth volume, *Neurology and Psychiatry*, of *The Practitioner's Library of Medicine and Surgery*, attention is very properly called to the fact that the ultimate welfare of the patient with a "nervous" disorder often depends upon the alertness and insight of the practitioner whom he first consults. To learn to appreciate the patient's personality make-up, and to recognize organic disease of the nervous system in its clinically incipient stage are the responsibilities of the physician toward this group of patients. Thirty-nine authors have contributed the forty-one chapters of this book. After sections in which the general principles of behavior, psychopathic personalities and their manifestations, and special methods of examina-

tion are considered, the individual affections of the nervous system are treated according to a grouping based upon etiological factors so far as is possible. This method brings together conditions in respect to which differential diagnosis is required and directs attention at once to such causal agencies as may be avoided or alleviated. Thus entire sections of from one to six chapters each are devoted to disease due to infection, to intoxication, to alimentary deficiency and to trauma.

It is quite impossible to attempt a critical evaluation of the individual sections of this book. In a general way it is evident that the editors have secured a degree of uniformity in style and a balance in treatment which is unusual in a work to which there have been so many contributors. Brief historical notes give added interest to many sections and well chosen illustrations have been freely used. To those practitioners who think that neurology and psychiatry are abstruse specialties, of but little application in their daily routine this volume can be enthusiastically recommended as readable, entertaining, informative and stimulating. It is a highly successful addition to *The Practitioner's Library*. C V W

Essentials of Psychopathology By GEORGE W. HENRY, M.D., Associate Professor of Psychiatry, Cornell University Medical School. ix + 312 pages. William Wood & Company, Baltimore. 1935. Price, \$4.00.

As the author says, "the study of psychopathology includes such a wide range of topics that it is difficult to select those most pertinent" to the understanding of the nature and causes of personality disorder. He has done well in his selection and in 12 chapters has concisely surveyed the subject. No matter how biased the reader may be, he will find a logical presentation of the factors in the evolution of personality. Sufficient case material is included to clarify his discussion. This book is not as verbose as the usual psychiatric textbook, although the author states that he has written it primarily for medical students and members of the medical profession.

Henry brings out the fact that "in spite of careful and extensive study of functional illness, no pathology of the brain has been disclosed. Furthermore the clinical manifestations of organic psychoses are little more than a caricature of the phenomena observed in functional psychoses. The sequence of emotional stresses which is so important in the evolution of personality disorders is usually irrelevant in organic illness. Just as mental illness is peculiar to human beings, so the associated phenomena would be possible only through the activity of a highly developed cerebral cortex."

The author proves the point that "with failure to take into consideration the psychogenic aspects of illness, not only do physicians make serious errors in diagnosis but their numerous examinations and their discussions at the bedside together with ill-advised medical and surgical treatment may accentuate the illness itself. Even when the physician is alert to these aspects he is inclined to divide the patients into two classes according to whether their illnesses are functional or organic. Such classification is necessarily inaccurate because there are psychogenic elements in all forms of illness, so that in order to understand and to deal effectively with any illness the physician must determine to what extent and under what circumstances psychogenic elements are present." On the other hand "no form of personality disorder offers immunity to physical illness."

In the X and XI chapters the author discusses psychiatric case records and methods of examination. Every physician should read these chapters in order to get some idea of the painstaking effort necessary to proper understanding of human nature. "Snap diagnosis" has no place in scientific medicine.

This is not a book of diagnosis, and the reader will not find listed the clinical entities or any of the various reaction types which occupy the attention of the psychiatrist, but he will find a most readable volume that may well supplement any textbook in medicine or surgery.

J. L. McC

AWARD OF THE JOHN PHILLIPS MEMORIAL MEDAL FOR 1936

DETROIT, MICHIGAN, MARCH 4, 1936

"After careful consideration by the Committee on Awards and upon its recommendation, the Board of Regents of the American College of Physicians has awarded the John Phillips Memorial Medal for 1936 to Dr Eugene Markley Landis

"Dr Landis exemplifies in his training and career and achievements the characteristics which this College wishes to encourage in American medicine and for the honor of which the award of this medal was established

"Dr Landis, though young in years, is already old in his experience in the special field of medical research which he has chosen. His contributions to scientific medicine have been numerous and important, and he holds a position of honor among his colleagues which has been recently recognized by his appointment as Assistant Professor in Medicine in the University of Pennsylvania

"The important contribution of Dr Landis has been in the field of capillary physiology and of edema. From this his interest has been extended to disturbances of the peripheral circulation, in which field he has made valuable contributions. He has devised new methods for testing these disturbances and for their treatment by a very original device of alternate suction and pressure. More recently he has been active in the study of renal disease in association with Professor Richards

"It is on the basis of these outstanding achievements that the award of the medal has been made to Dr Landis, and I have the honor and the privilege, on behalf of the Board of Regents, to bestow upon you, Dr Eugene Markley Landis, the John Phillips Memorial Medal for 1936 "

Presentation address by Dr James Alex Miller, President of the American College of Physicians at the Annual Convocation

COLLEGE NEWS NOTES

The following Fellows of the College have become Life Members, making a total of 61 to date

Dr Anna Weld, Rockford, Ill
Dr Estes Nichols, Portland, Maine
Dr William H Watters, Miami, Fla

GIFTS TO THE COLLEGE LIBRARY

Dr J W Torbett (Fellow), Marlin, Texas—one book, "Pastime Poems of a Busy Doctor" Dr Torbett's book is autographed "To the Doctors of the American College of Physicians"

Dr William R Brooksher (Fellow), Fort Smith, Ark—one reprint
Dr Gerald M Cline (Fellow), Bloomington, Ill—one reprint
Dr Archibald L Hoyne (Fellow), Chicago, Ill—two reprints
Dr Manfred Kraemer (Fellow), Newark, N J—seven reprints
Dr William LeFevre (Fellow), Muskegon, Mich—one reprint
Dr Alfred J Scott, Jr (Fellow), Los Angeles, Calif—one reprint
Dr Sidney A Slater (Fellow), Worthington, Minn—two reprints
Dr Ramon M Suarez (Fellow), Santurce, P R—two reprints
Dr John W Williams (Fellow), Cambridge, Mass—eighteen reprints
Dr Robert B Wood (Fellow), Knoxville, Tenn—one reprint
Dr Jacob Greenstein (Associate), Providence, R I—one reprint

Dr Herbert T Kelly (Fellow), Philadelphia, Pa, was guest speaker, February 5, at the meeting of the Luzerne County Medical Society at Wilkes-Barre, Pa, his subject being "The Early Diagnosis and Treatment of Diabetes"

Dr Robert B Radl (Fellow), formerly Physician, Students' Health Service, University of Minnesota, and Assistant Professor in the Department of Preventive Medicine and Public Health, University of Minnesota Medical School, is now associated with the Quam and Ramstad Clinic at Bismarck, N D

Dr John Russell Twiss (Fellow), New York City, Associate in Medicine, New York Post-Graduate Medical School and Hospital, Columbia University, has recently become Assistant Attending Physician, Gouverneur Hospital

Dr William C Voorsanger (Fellow) has been appointed to the Health Advisory Board of the City and County of San Francisco

Dr Raymond W Swinnev (Fellow) is chief of the medical staff of the Long Beach Community Hospital and has recently been elected Secretary of the Harbor Branch of the Los Angeles County Medical Society

Under the Governorship of Dr L E Viko, the Utah members of the American College of Physicians held a sectional meeting at Salt Lake City during the latter part of January

Under the Governorship of Dr Adolph Sachs, members of the American College of Physicians held a sectional meeting for the State of Nebraska on January 30, 1936, at Omaha Dr Augustus Pohlmán, Professor of Anatomy at Creighton University Medical College, addressed the group on "The Physiology of the Lymphatic System" Forty members were present, various committees were appointed and a plan drawn up for meetings each year, alternating between Omaha and Lincoln

Dr Albert A Raymond has resigned from the Rockefeller Institute of Medical Research with which he had been connected for the past nine years to accept the appointment as Director of the Research Laboratories of G D Searle & Co, Chicago

Dr William D Weis (Fellow), Crown Point, Ind, is Health Commissioner of Lake County Lake County is the first and only County in the State of Indiana having an all-time Health Department personnel consisting of the Health Commissioner, Sanitary Inspector, four nurses and a clerk

The Thirty-Second Annual Congress on Medical Education, Medical Licensure and Hospitals was held at Chicago, February 17 and 18, 1936 Fellows of the College who contributed to the program appear below

Dr Walter L Bierring, Des Moines, Iowa—"Consistency versus Chaos in Medical Education and Licensure"

Dr James S McLester, Birmingham, Ala—"The Personal Characteristics of the Teacher"

Dr Nathan B Van Etten, New York, N Y—"What Is the Social Objective of the Young Physician?"

Dr William D Cutter, Chicago, Ill—"The Federation and the Survey of Medical Schools"

Dr Harold Rypins, Albany, N Y—"Final Objective—The Federation of State Medical Boards"

Dr Howard T Karsner, Cleveland, Ohio—"The Laboratory of Pathology in the Small Hospital"

Dr W McKim Marriott, St Louis, Mo—"Newer Points of View Concerning the Use of the Outpatient Department in Medical Education"

Dr Arthur C Morgan, Philadelphia, Pa—"Aggressive versus Passive Attitudes of State Board Members"

Other Fellows of the College who participated in the official discussions or as presiding officers included Dr Merritt W Ireland, Washington, D C, Dr Waller S Leathers, Nashville, Tenn, Dr Roscoe L Sensenich, South Bend, Ind, Dr Wilburt C Davison, Durham, N C, Dr John Wyckoff, New York, N Y, and Dr Wilbard C Rappleye, New York, N Y

Drs Anthony Bassler (Fellow), Max Einhorn (Fellow) and Samuel Weiss (Fellow) have been selected as the three American physicians who have been named

honorary members of the Belgian Gastroenterological Society. All three are also Fellows of the National Society for the Advancement of Gastroenterology.

Dr. Anthony Bassler (Fellow) has been elected President of the National Society for the Advancement of Gastroenterology, President of the American Committee and United States Delegate to the International Society of Gastroenterology and Vice-Chairman of the Gastroenterological Section of the Pan American Congress.

Dr. Joseph H. Barach (Fellow), Pittsburgh, Pa., has been elected a member of The Society of the Sigma Xi.

ELECTIONS TO FELLOWSHIP

December 15, 1935

<i>Candidates</i>	<i>Sponsors</i>
	ALABAMA
James Alto Ward, Birmingham	William C. Blake, A. B. Craddock, Fred W. Wilkerson
James Harold Watkins, Montgomery	C. C. Bass, Philip H. Jones, John H. Musser, Fred W. Wilkerson
	ARIZONA
Virgil Guy Presson, Tucson	S. C. Davis, Charles S. Kibler, W. Warner Watkins
	ARKANSAS
Jesse Dean Riley, State Sanatorium	F. O. Mahony, George B. Fletcher, Oliver C. Melson
	CALIFORNIA
Eaton MacLeod MacKay, La Jolla	Burrell O. Raulston, E. Richmond Ware, F. M. Pottenger, James F. Churchill
Rudolph Herbert Sundberg, San Diego	Lvell C. Kinney, C. Ray Lounsberry, James F. Churchill
Percival Allen Grav, Jr., Santa Barbara	William D. Sansum, Harry E. Henderson, James F. Churchill
Robert Ammiel Hare, Santa Barbara	William D. Sansum, Franklin R. Nuzum, James F. Churchill
	COLORADO
Ward Darlev, Denver	Clough T. Burnett, James R. Arneill, Gerald B. Webb
	CONNECTICUT
Robert S. Starr, Hartford	J. Elder Hutchison, G. Gardiner Russell, Henry F. Stoll
Samuel Julius Chernaik, New Britain	C. Brewster Brainard, O. G. Wiedman, Henry F. Stoll

*Candidates**Sponsors*

William Barclay Jerhune, Jr, New Canaan	Charles Burlingame, Francis G. Blake, Henry F. Stoll
Arthur Hartt Jackson, Washington	Francis G. Blake, O. G. Wiedman, Henry F. Stoll

MEDICAL CORPS, U. S. ARMY

George C. Beach, Fort Leavenworth, Kan.	Charles R. Reynolds
Coleridge Livingstone Beaven, Denver, Colo.	E. I. Cook, William C. Pollock, Charles R. Reynolds
Samuel McPherson Browne, San Antonio, Tex.	Charles R. Reynolds
George Burgess Foster, Jr, Denver, Colo.	Charles R. Reynolds
Frederick Hultman Foucar, Washington, D. C.	Wallace M. Yater, Raymond O. Dart, Charles R. Reynolds
Arthur Raymond Gaines, Denver, Colo.	E. L. Cook, William C. Pollock, Charles R. Reynolds

MEDICAL CORPS, U. S. NAVY

Clyde Wyndham Brunson, San Pedro, Calif.	C. S. Butler, Percival S. Rossiter
Lyle J. Roberts, Washington, D. C.	Paul F. Diekens, W. W. Haigrave, Percival S. Rossiter
William Wayne Wickersham, Philadelphia, Pa.	Walter M. Anderson, John H. Chambers, Percival S. Rossiter

DISTRICT OF COLUMBIA

William McCormick Ballinger, Washington	Wm. Gerry Morgan, Tomas Cuygas, Wallace M. Yater
John A. Reed, Washington	William J. Mallory, William A. White, Wm. Gerry Morgan, Wallace M. Yater

FLORIDA

Kenneth Phillips, Miami	William Henry Watters, P. B. Welch, Turner Z. Cason
-------------------------	---

ILLINOIS

Emil Weiss, Chicago	Isadore M. Trace, Maximilian J. Hubeny, James G. Carr
Maxim Pollak, Peoria	William H. Walsh, George Parker, Samuel E. Munson
Harold Conrad Ochsner, Waukegan	H. Milton Conner, Arthur E. Mahle, James G. Carr

IOWA

Elmer E. Kottke, Des Moines	John H. Peek, Tom B. Throckmorton, Walter L. Bierring
-----------------------------	---

KENTUCKY

Carl Hale Fortune, Lexington	Charles N. Kavanaugh, John Harvey, Chauncey W. Dowden
George Earle Wakerlin, Louisville	J. Murray Kinsman, John Walker Moore, Chauncey W. Dowden
Benjamin Lane Brock, Waverly Hills	J. Murray Kinsman, Morris Flexner, Chauncey W. Dowden

*Candidates**Sponsors*

LOUISIANA

Thomas Everett Strain, Shreveport
 Clarence Hungerford Webb, Shreveport

W S Kerlin, T E Williams, Joseph E Knighton
 T P Lloyd, D H Duncan, Joseph E Knighton

MAINE

Edward Alfred Greco, Portland

Francis J Welch, John R Hamel, Edwin W Gehrung

MASSACHUSETTS

Gerardo M Balboni, Boston

Chester M Jones, Donald S King, James H Means,
 William B Breed

Reginald Fitz, Boston

Charles F Martin, James H Means, Roger I Lee
 Laurence D Chapin, George L Steele, William B Breed

Allen Sheppard Johnson, Springfield

Horace Kimball Richardson, Stock-
 bridge

Austen Fox Riggs, Sydney R Miller, James Alex
 Miller, William B Breed

MICHIGAN

Harold Riche Roehm, Birmingham

Walter M Simpson, Carl V Weller, James D Bruce
 William H Gordon, Henry R Carstens, James D Bruce

Harold Abraham Robinson, Detroit

MINNESOTA

Dwight Locke Wilbur, Rochester

George E Brown (Deceased), E V Allen, Edward L Tuohy

Russell M Wilder, Rochester

George E Brown (Deceased), Herbert Z Giffin,
 Edward L Tuohy

MONTANA

Ferdinand Ripley Schemm, Great Falls

Harold W Gregg, Ernest D Hitchcock, Louis H Fligman

NEBRASKA

Frank Lowell Dunn, Omaha

J A Henske, John R Klevla, Adolph Sachs

NEVADA

Lawrence Parsons, Reno

John C Ruddock, William H Leake, Egerton L Crispin

NEW JERSEY

Manfred Kraemer, Newark

Edward C Klein, Jr, Lewis W Brown, Clarence L Andrews

NEW YORK

Max Mensch, Brooklyn

Philip I Nash, Thomas J Longo, Luther F Warren,
 Robert A Cooke

Samuel Arthur Vogel, Buffalo

Nelson G Russell, A H Aaron, Allen A Jones
 Luvia Willard, Marshall C Pease, Luther F War-
 ren, Robert A Cooke

Ida J Mintzer, Jamaica

Robert L Levy, New York

Walter W Palmer, Willard C Rappleye, Robert A Cooke

James Rubeo Lisa, New York

David S Likely, Harlow Brooks, Robert A Cooke

*Candidates**Sponsors*

Howard Francis Shattuck, New York
R Garfield Snyder, New York

Arthur F Chace, W P Anderton, Robert A Cooke
Harlow Brooks, Emanuel Libman, Robert A Cooke

NORTH CAROLINA

George Curtis Crump, Asheville

A B Craddock, Walter R Johnson, Charles H
Cocke

William Ray Griffin, Asheville

Paul H Ringer, Walter R Johnson, Charles H
Cocke

Ronda Horton Hardin, Banner Elk

Coate L Sherrill, James W Vernon, Charles H
Cocke

Duncan Waldo Holt, Greensboro

Wingate M Johnson, J K Pepper, Charles H
Cocke

James W Dickie, Southern Pines

P P McCain, Paul H Ringer, Charles H Cocke

OHIO

Frank J Dorin, Cleveland

Richard Dexter, Edgar P McNamee, A B Brower

Joseph Marchant Hayman, Jr, Cleveland

Thomas Fitz-Hugh, Jr, Alfred Stengel, A B
Brower

ORIGON

George Wilber Millett, Portland

John H Fitzgibbon, Homer P Rush, T Homer
Coffen

PENNSYLVANIA

Ruth Walker Wilson, Beaver

R R Snowden, C Howard Marcy, E Bosworth
McCready

Nathan Blumberg, Philadelphia

Joseph C Doane, A M Ornstein, E J G Beardslev

Nathan Harry Einhorn, Philadelphia

Leonard G Rowntree, Judson Daland, E J G
Beardslev

Samuel G Shepherd, Philadelphia

James E Talley, Joseph T Beardwood, Jr, William
D Stroud, E J G Beardslev

TEXAS

Earl Jones, Brownwood

I C Terrell, John G Young, Charles T Stone

Henry Franklin Carman, Dallas

Henry M Winans, C M Grigsby, Charles T Stone

VIRGINIA

Harold Walter Potter, Newport News

Walter B Martin, Beverley R Tucker, J Morrison
Hutcheson

Wyndham Bolling Blanton, Richmond

R Finley Gayle, Jr, Dean B Cole, J Morrison
Hutcheson

Douglas Gordon Chapman, Richmond

Charles M Cravatt, Dean B Cole, J Morrison
Hutcheson

WISCONSIN

Guy Walter Carlson, Appleton

Otho A Fredler, Friedrich Eigenberger, Rock
Sleyster

CANADA

Alberta

Percy Harry Sprague, Edmonton

Albert M Snell, F A Willius, Edward L Tuohy

*Candidates**Sponsors*

MEXICO, D F

Fernando Ocaranza, Mexico City

William D Nimeh, John J Sparks, Charles T Stone

CHINA

Mason Pressly Young, Soochow

P P McCain, Edgar A Hines, Robert Wilson

SYRIA

Edward Lewis Turner, Beirut

Joseph L Miller, George H Coleman, Arthur R Elliott

ELECTIONS TO ASSOCIATESHIP

December 15, 1935

ALABAMA

James Bowron McLester, Birmingham

Groesbeck Walsh, H Cliff Sauls, Fred W Wilkerson

CALIFORNIA

Bernard Edward McGovern, San Diego

William Egbert Robertson, Gerald B Webb, Francis M Pottenger, James F Churchill

Thomas Hodge McGavack, San Francisco

Dudley W Bennett, Stacy R Mettier, William J Kerr, Hans Lisser

Edwin Eugene Ziegler, San Francisco

Marius B Marcellus, Audley O Sanders, Hans Lisser, Charles M Griffith

COLORADO

Paul A Draper, Colorado Springs

A Lee Briskman, John A Sevier, Gerald B Webb

Henry Wendell Maly, Colorado Springs

A Lee Briskman, John A Sevier, Gerald B Webb

William Corr Service, Colorado Springs

G Burton Gilbert, John A Sevier, Gerald B Webb

CONNECTICUT

John S Staneslow, Waterbury

John H Foster, J Harold Root, Henry F Stoll

Maurice Timothy Root, West Hartford

J Elder Hutchison, John A Wentworth, Henry F Stoll

MEDICAL CORPS, U S ARMY

James Brent Anderson, Fort Sam Houston, Tex

William H Allen, Henry C Coburn, Jr, Charles R Reynolds

Forrest Ralph Ostrander, Fort Sam Houston, Tex

William H Allen, Henry C Coburn, Jr, Charles R Reynolds

Stuart Gross Smith, Denver, Colo

Everett L Cook, William C Pollock, Charles R Reynolds

John M Welch, Washington, D C

Charles R Reynolds

Dwight Moody Young, Denver, Colo

William C Pollock, Everett L Cook, Charles R Reynolds

MEDICAL CORPS, U S NAVY

George Arthur Cann, San Diego, Calif

Edward C White, Walter A Vogelsang, Percival S Rossiter

*Candidates**Sponsors*

U S PUBLIC HEALTH SERVICE

Ralph Emmett Porter, Fort Stanton, N M	Meldrum K Wylder, J R Van Atta, LeRoy S Peters, Hugh S Cumming
Thomas Haze Tomlinson, Jr, Fort Stanton, N M	Meldrum K Wylder, LeRoy S Peters, Hugh S Cumming

DISTRICT OF COLUMBIA

Frank Stephen Horvath, Washington	James Alexander Lyon, Tomas Cajigas, Wallace M Yater
George Louis Weller, Jr, Washington	Walter A Bloedorn, Walter Freeman, William Gerry Morgan, Wallace M Yater

FLORIDA

William Glenn Post, Jr, St Petersburg	Roscoe H Knowlton, Arnold S Anderson, T Z Crison
---------------------------------------	--

GEORGIA

Lancelot Minor Blackford, Atlanta	John B Fitts, H Cliff Sauls, Glenville Giddings
William Howell Kiser, Jr, Atlanta	John B Fitts, H Cliff Sauls, Glenville Giddings
William Rudy Minnich, Atlanta	John B Fitts, H Cliff Sauls, Glenville Giddings
Thomas Fort Sellers, Atlanta	John B Fitts, H Cliff Sauls, Glenville Giddings
Carter Smith, Atlanta	H Cliff Sauls, John B Fitts, Glenville Giddings
Richard Blanton Wilson, Atlanta	John B Fitts, H Cliff Sauls, Glenville Giddings
Hartwell Joiner, Gainesville	John B Fitts, H Cliff Sauls, Glenville Giddings

ILLINOIS

Clarence J McMullen, Oak Park	Hugh A McGuigan, Arthur E Mahle, James G Carr
Emmet Forrest Pearson, Springfield	Jacob J Singer, Alfred Goldman, David P Barr, Samuel E Munson

IOWA

Richard Oscar Pfaff, Des Moines	Harry A Collins, Edward W Anderson, Walter L Bierring, Tom B Throckmorton
Fred Sternagel, Valley Junction	John H Peck, Christian B Luginbuhl, Walter L Bierring

KANSAS

Fred Ernest Angle, Kansas City	Peter T Bohan, Howard E Marchbanks, Thomas T Holt
--------------------------------	---

KENTUCKY

Marion Foree Beard, Louisville	J Murray Kinsman, John Walker Moore, Chauncey W Dowden
Max L Garon, Louisville	Morris Flexner, J Murray Kinsman, Chauncey W Dowden

MASSACHUSETTS

Thomas Sterling Claiborne, Boston	Lewis M Hurvathal, Frank N Allan, William B Breed
Milton James Quinn, Winchester	Frederick T Lord, Donald S King, James H Means, William B Breed

*Candidates**Sponsors*

MICHIGAN

Bruce Hutchinson Douglas, Detroit

William A. Evans, Lawrence Reynolds, Charles G. Jennings, James D. Bruce

David J. Sandweiss, Detroit

William H. Gordon, Hugo A. Freund, James D. Bruce

MINNESOTA

William Arnold Stafne, Moorhead

George E. Brown (deceased), Bayard T. Horton, Edward L. Tuohy

Howard Miller Odel, Rochester

George B. Eusterman, Henry W. Woltman, Edward L. Tuohy

Martin Van Buren Teem, Rochester

Bayard T. Horton, Harry L. Smith, Edward L. Tuohy

MISSOURI

Hyman I. Spector, St. Louis

Daniel L. Sexton, Joseph F. Bredeck, David P. Barr, A. Comingo Griffith

NEBRASKA

Joseph Daniel McCarthy, Omaha

Warren Thompson, John R. Kleyla, Adolph Sachs

NEW JERSEY

Harold Korb Eynon, Collingswood

Grant O. Favorite, Dunne W. Kirby, William D. Stroud, Clarence L. Andrews

Louis Leo Perkel, Jersey City

Abraham E. Jaffin, Berthold S. Pollak, Clarence L. Andrews

NEW YORK

Charles S. Byron, Brooklyn

Simon R. Blatteis, Henry Joachim, Luther F. Warren, Robert A. Cooke

Paul Chadbourne Eschweiler, Brooklyn

Frank Bethel Cross, Joshua M. Van Cott, Robert A. Cooke

Mendel Jacoby, Brooklyn

Maurice J. Dattelbaum, Irving J. Sands, Luther F. Warren, Robert A. Cooke

William August Lange, Brooklyn

Eugene S. Dalton, Foster Murray, James Alex. Miller, Robert A. Cooke

Bernard Sternberg, Brooklyn

David Gingold, Henry Joachim, Luther F. Warren, Robert A. Cooke

John Josiah Maisel, Buffalo

George E. Brown (deceased), Fredrick A. Willius, Edward L. Tuohy, Allen A. Jones

Nelson W. Strohm, Buffalo

Nelson G. Russell, Carroll J. Roberts, Allen A. Jones

Alexander Scott Dowling, Corning

Howard T. Karsner, Carl J. Wiggers, Allen A. Jones

Harry Clifford Oard, Jamaica

Carl Boettiger, Ernest E. Keet, Luther F. Warren, Robert A. Cooke

Louis Ashley Van Kleeck, Manhasset

Carl Boettiger, Goodwin A. Distler, Luther F. Warren, Robert A. Cooke

Anthony C. Cipollaro, New York

Walter G. Lough, David Stanley Likely, Robert A. Cooke

Julia V. Lichtenstein, New York

Henry T. Chickering, Carl H. Greene, James Alex. Miller, Robert A. Cooke

Cornelius Horace Traeger, New York

Harlow Brooks, Emanuel Libman, Robert A. Cooke

*Candidates**Sponsors*

NORTH CAROLINA

Julian Meade Ruffin, Durham

Paul F Whitaker, William B Kinlaw, Charles H Cocke

Edward Sandling King, Wake Forest

Verne S Caviness, Thurman D Kitchin, Charles H Cocke

OHIO

Charles S Greene, Canton

Joseph H Barach, Hiram B Weiss, A B Brower

Dale Pettigrew Osborn, Cincinnati

Oscar Berghausen, Jacob L Tuechter, A B Brower

William Orville Ramey, Cincinnati

David A Tucker, Jr, John H Skavlem, A B Brower

Fay Atkinson McFevre, Cleveland

Henry J John, Charles L Hartsock, A B Brower

Morris Deitchman, Youngstown

William H Bunn, Colin R Clark, A B Brower

OKLAHOMA

John B Morey, Ada

George E Brown (deceased), Nelson W Barker, Lea A Riel

Ralph Bowen, Oklahoma City

Henry H Turner, Lewis J Moorman, Lea A Riel

Homer Albert Rupprecht, Tulsa

Russell C Pigford, William J Bryan, Jr, Lea A Riel

OREGON

Willard Fletcher Hollenbeck, Portland

John H Fitzgibbon, Homer P Rush, T Homer Coffen

Merle W Moore, Portland

Homer P Rush, Frank R Mount, T Homer Coffen

PENNSYLVANIA

Robert Sloan Lucas, Butler

Jacob C Atwell, Lester Hollander, E Bosworth McCready

Constantine P Faller, Harrisburg

Jesse L Lenker, S Calvin Smith, E J G Beardsley

John O Woods, New Castle

Wayne W Bissell, Eliah Kaplan, E Bosworth McCready

John Trimble Eads, Philadelphia

Edward S Dillon, Samuel B Scholz, Jr, E J G Beardsley

Harold R Keeler, Philadelphia

Thomas Klein, Charles C Wolferth, George Morris Piersol, E J G Beardsley

Charles Fay Nichols, Philadelphia

Thomas Klein, Russell S Boles, William D Stroud, E J G Beardsley

RHODE ISLAND

Earl Francis Kelley, Pawtucket

John F Kenney, Charles F Gormly, Alexander M Burgess

Russell Stanton Bray, Providence

Herman A Lawson, Isaac Gerber, Alexander M Burgess

SOUTH CAROLINA

Francis Eugene Zemp, Columbia

J Heyward Gibbes, Hugh Smith, Robert Wilson

TEXAS

William Bluford Adamson, Abilene

Erle D Sellers, Frederick E Hudson, Charles T Stone

Candidates

James John Gorman, El Paso
 Joseph Fielding McVeigh, Fort Worth
 Edward Randall, Jr, Galveston
 Frances Ralston Vanzant, Houston

William Grady Mitchell, San Angelo

Julian Cox Barton, San Antonio
 William Walton Bondurant, San Antonio

Edgar Marion McPeak, San Antonio
 David Robert Sacks, San Antonio

James Newton Williams, Richmond

Cecil Loveland Morrow, Seattle

Dudley Curtis Ashton, Beckley

Charles B Chapman, Welch
 Howard Russell Sauder, Wheeling

Marcos Fernan-Nunez, Milwaukee
 John C Grill, Milwaukee

Sponsors

Orville E Egbert, James W Laws, Charles T Stone
 Will S Horn, Truman C Terrell, Charles T Stone
 Titus H Harris, Boyd Reading, Charles T Stone
 Walter C Alvarez, George B Eusterman, Edward
 L Tuohy

Albert W Bromer, Ross V Patterson, William D
 Stroud, E J G Beardsley

Lee Rice, John H Musser Charles T Stone
 Lee Rice, Joe Kopecky, Charles T Stone

Lee Rice, Hugh J Morgan, Charles T Stone

Lee Rice, George R Herrmann, Charles T Stone

VIRGINIA

R Finley Gavle, Jr, Dean B Cole, J Morrison
 Hutcheson

WASHINGTON

Charles E Watts, Delbert H Nickson, Frederick
 Epplen (deceased)

WEST VIRGINIA

J Morrison Hutcheson, R Finley Gavle, Jr, John
 N Simpson

Albert M Snell, James F Weir, John N Simpson
 Delivan A MacGregor, John A Toomey, John N
 Simpson

WISCONSIN

Francis D Murphv, William J Egan, Rock Sleyster
 Joseph Lettenberger, Francis D Murphy, Rock
 Sleyster

OBITUARIES

DR JOHN LEONARD ECKEL

From the Encyclopedia of American Biography we learn that our much beloved confrere, Dr John Leonard Eckel, who died November 26, 1935, was born in Perrysburg, Ohio, April 28, 1880. He graduated in medicine at the School of Medicine, University of Buffalo, in 1907. He interned at the East Manhattan State Hospital, New York City, and was Junior Assistant Physician there in 1908-09. He held the same post at the Buffalo State Hospital, 1909-10, and was senior assistant physician at the same hospital, 1910-11. September 1911, he went to the University of Berlin and worked in nervous and mental diseases for two semesters under Professors Oppenheim, Ziehen and Jacobson. He also worked in the University of Munich under Professors Alzheimer and Kraepelin. He spent one semester at the University of London, Queen's Square Hospital, for nervous and mental diseases under Professors Gordon Holmes, S. A. K. Wilson, Farquhar, Buzzard, Purves Stewart and Frederick Batten. Returning to Buffalo in 1913, he began a practice limited to nervous and mental diseases and was soon put on the roster of the Medical School of the University of Buffalo. He was Associate Professor of Neurology and Assistant Professor of Psychiatry.

Dr Eckel went to Vienna for further scientific research and clinical work under Professor Wagner von Jauregg and his assistants, Pappenheim and Schilder. His research work was done with Professor Otto Marburg, Director of the Neuropathological Laboratory. It was there Dr Eckel's research work "Encephalitis Acutissima" was published in the "Jahrbuch" in January 1926. This was an outstanding bit of work which was widely quoted, referred to and favorably mentioned in European medical journals. He did much research work with Dr N. W. Winkelman of the University of Pennsylvania and Temple University, Philadelphia, going to Philadelphia every month for over 15 years. Several of the most valuable articles he wrote were in collaboration with Dr Winkelman.

Dr Eckel was attending and consulting neurologist and psychiatrist to the Buffalo General Hospital, Millard Fillmore Hospital, Memorial Hospital, Our Lady of Victory Hospital, Buffalo City Hospital, Sister's Hospital, Providence Retreat, Crippled Children's Guild, Emergency Hospital and J. N. Adam Memorial Hospital at Perrysburg, N. Y.

He was a member of the American College of Physicians, The Buffalo Academy of Medicine, Erie County and New York State Medical Societies, American Medical Association, American Psychiatric Association, American Neurological Association, American Association for Research in Nervous and Mental Diseases, New York Neurological Society, Philadelphia Neurological Society, Central Neuro-Psychiatric Association, Buffalo

Neuro-Psychiatric Society, Pan-American Medical Association and the American Association for the Advancement of Science and held important offices in many of these organizations

Dr Eckel was asked to read papers at the following meetings the British and American Neurological Societies, London, July 28, 1927, the First International Congress on Neurology in Berne, Switzerland, September 3, 1931, the Pan-American Medical Congress in Dallas, Texas May, 1933, the Pan-American Floating Congress, March, 1934, the Second International Congress on Neurology in London, August 1, 1935, etc

During the World War, Dr Eckel held the commission of Captain in the U S Army

He was a member of the Saturn Club, the University Club, the Buffalo Club, the Torch Club and many other social and fraternal organizations

John Leonard Eckel had personal charm of manner which won many friends He was sound in his work and practice and thorough in his clinical approach, possessed of a sunny nature with a winning smile and presence, comforting to the sick, yet, withal, inspiring confidence and trust

His death was almost a tragedy He apparently did not realize he was ill but had precordial and epigastric pain a few days before his sudden death He went, however, to see some of his patients and while sitting beside one of them while two nurses stood by, according to the account given in the *Courier-Express*, "he straightened in his chair, sighed and died"

ALLEN A JONES, M D , F A C P ,

Governor for Western New York

DR HENRY FINLAY HYNDMAN

Dr Henry Finlay Hyndman (Associate), Wichita, Kansas, died on October 31, 1935, of diabetes mellitus, aged, 49 years

Dr Hyndman was born in Adrian, Illinois, May 4, 1886 He received the degree of Bachelor of Arts from the University of Kansas, in 1908, and the degree of Doctor of Medicine from the Medical School of that institution in 1910

Dr Hyndman devoted his practice to internal medicine but was especially interested in diabetes He was a member of the staff of St Luke's Hospital, Wellington, Kansas, 1911-18, member of staff, Wichita Hospital, 1918 to date, chief of service and member of Executive Council of the staff of Sedgwick County Charity Hospital of Wichita, from 1933 to date, and a member of the medical service and President of Staff of Wesley Hospital, Wichita, from 1929 to date He was a member, also, of the Sedgwick County Medical Society, Kansas State Medical Society, Nu Sigma Nu Fraternity, a Fellow of the American Medical Association, and had been an Associate of the American College of Physicians since December 16, 1934

"Dr Hyndman stood for and practiced the highest principles in his profession. He loved his work and was unwavering in his endeavor to live up to the professional code of ethics. He was never heard to speak disparagingly of any colleague's work or character. Basically he was one of that group of disappearing physicians—the family doctor. Of recent years, however, he devoted most of his time to the care of diabetics and was one of the foremost men in this type of work in Kansas. Our Society has lost an enthusiastic and progressive member and we all have lost a dear friend, and a counsellor"—Medical Bulletin of The Sedgwick County Medical Society

DR WILLIAM KRAUSS

Dr William Krauss (Fellow), Meridian, Miss., died December 21, 1935, in the Gartly-Ramsay Hospital, Memphis, of carcinosis originating in x-ray burns of the hand, aged, 74 years.

Dr Krauss was born in Bavaria. He graduated from the Memphis College of Pharmacy in 1883. He then attended the Memphis Hospital Medical College, graduating in 1889. He pursued postgraduate study in histology, pathology and bacteriology at the University of Kiel and at the University of Wurzburg. He was successively Assistant in Anatomy, Instructor in Chemistry, Histology, Pathology and Bacteriology at the Memphis Hospital Medical College between 1890 and 1903. He became Dean and Professor of Pathology in the Medical Department of the University of Mississippi, 1909–10, after having served as Professor of Pathology and Tropical Medicine in the College of Physicians and Surgeons Memphis, 1906–09. From 1912 to 1929, he was Professor of Tropical Medicine at the University of Tennessee College of Medicine. He was at one time Secretary of the Board of Health of Memphis, also, acting Assistant Surgeon in the U. S. Public Health and Marine Hospital Service, serving as diagnostician during the yellow fever epidemic in 1897–98 and in 1905. At one time he was Director of Laboratories, Memphis City Health Department, and just previous to his death had been with the Stingily Laboratories, Meridian, Miss., in the capacity of Director of the x-ray department and of the laboratories proper.

Dr Krauss was a past President of the Memphis and Shelby County Medical Society, a past President of the West Tennessee Medical and Surgical Association, a member of the Mississippi State Medical Society, Southern Medical Association and the American Medical Association.

At various times he served on the staffs of the Memphis General, Baptist and St. Joseph's Hospitals, all of Memphis. He was a former Chairman of the National Malaria Commission and Chairman of the Tennessee Pellagra Commission. Dr Krauss became a Fellow of the American College of Physicians during 1919.

DR GEORGE WASHINGTON McCASKEY

Dr George Washington McCaskey (Fellow), Fort Wayne, Ind., died December 30, 1935, of cerebral hemorrhage and cerebral arteriosclerosis, aged, 82 years

Dr McCaskey was born at Delta, Ohio, graduated from the Jefferson Medical College of Philadelphia in 1877 and began practice in Fort Wayne, Ind., in 1882. He became an outstanding diagnostician and was nationally known as an authority on diseases of the stomach. For a number of years he served as professor of the theory and practice of medicine in the old Fort Wayne Medical College. He was professor emeritus of medicine at the Indiana University School of Medicine in Indianapolis.

Dr McCaskey was a member and past president of the Indiana State Medical Association, a member and past president of the northern Tri-State Medical Association, a member of the American Medical Association, the American Gastro-Enterological Association and had been a Fellow of the American College of Physicians since June 5, 1917. He was the author of more than one hundred publications.

DR STEPHEN R PIETROWICZ

Stephen R. Pietrowicz, a Fellow of the College since 1920, died January 12, 1936. Dr. Pietrowicz was born in Posen, Poland, August 23, 1873. He attended St. Mary Magdalene Gymnazium, Posen, Poland. In his young manhood he came to America where he continued his education at St. Stanislaus College, Chicago, and at the College of Physicians and Surgeons of Chicago, School of Medicine, University of Illinois, from which he received his medical degree in 1898.

Since that time he was engaged in practice in Chicago, for many years devoting special attention to internal medicine. He was attending physician at St. Mary's of Nazareth Hospital in Chicago from 1900 to 1908, physician-in-chief of the same hospital from 1908 to 1925, and president of the staff and senior attending physician from 1925 to the time of his death.

He served as attending physician at Cook County Hospital from 1911 to 1913. He was superintendent of the Chicago State Hospital in 1912. From 1911 to 1917 he was senior professor of medicine at the Chicago College of Medicine and Surgery. From 1918 to 1920 associate in medicine, University of Illinois. Thereafter, until the time of his death he was clinical professor of medicine, Loyola University School of Medicine.

He was a member of the school board of Chicago at one time. He held membership in the Society of Internal Medicine of Chicago, the Institute of Medicine, Chicago, the Chicago Medical Society, Illinois Medical Society, American Medical Association, Chicago Pathological Society, Polish Medical Society, Chicago Tuberculosis Institute.

Through many years Dr Pietrowicz carried on a very busy and extensive practice. He gave much of his time to his work in the hospital and medical school. His interest in St. Mary's of Nazareth Hospital was especially great and he rendered a service which will long be remembered. Deeply interested in his life work, he gave himself without stint to those who came under his care.

JAMES G. CARR, M.D., F.A.C.P.
Governor for Northern Illinois

DR. CHARLES CRAWFORD HINTON

Dr. Charles Crawford Hinton (Fellow), Macon, Georgia, died suddenly of coronary artery disease on February 25, 1936, aged 47.

Dr. Hinton was born at Milledgeville, Georgia, October 1, 1888. He attended the public schools of Bibb County and entered Emory University, now at Atlanta but then at Oxford, Georgia, graduating with the degree of B.Ph. in 1909. He thereafter entered the medical department of Johns Hopkins University School of Medicine, graduating in 1913. His internship was spent in a Baltimore hospital, whereupon he became Assistant in Medicine and Chief of the Out-Patient Department Clinics of Emory University. In 1916 he became Associate in Medicine at Emory University, remaining until 1917. From 1919 until the time of his death, he was Laboratory Consultant to the U. S. Veterans Administration at Macon, and from 1920 until the time of his death, he was Internist to the Middle Georgia Sanatorium. He was a former president of the Macon Medical Society of Bibb County, a member of the Southern Medical Association, the American Medical Association and the Clinical Society of Middle Georgia Sanatorium. He had been a Fellow of the American College of Physicians since 1929.

ANNALS OF INTERNAL MEDICINE

VOLUME 9

APRIL, 1936

NUMBER 10

THE CHANGING ORDER IN MEDICINE ~

By JAMES ALEXANDER MILLER, A M , M D , F A C P , *New York, N Y*

I WOULD be very neglectful of my opportunity and very untrue to my deep feelings if I failed upon this occasion to record my great appreciation of the progress the American College of Physicians has made and is making in the rôle of leadership in the field of internal medicine, and also my very deep and heartfelt appreciation of the privilege and honor which has been conferred upon me in my selection to preside over the activities of the College during the past year

College Matters This year has been fruitful in accomplishments The affairs of the College have continued to prosper, and this is due in no small measure to the faithful devotion of the Board of Regents and Governors and particularly to the extraordinary faithfulness and ability of our executive staff under the leadership of Mr Loveland

Our main function, that of postgraduate education, was notably furthered at our Philadelphia meeting, and this meeting which we are holding in Detroit is also a notable landmark in our progress We have met here under a cloud of sorrow caused by the sudden death of our beloved associate Dr Charles G Jennings who, before his untimely end, had already organized the clinical program which we have been enjoying, and whose devotion to the highest ideals of the College has been notable during many years of service upon our Board of Regents His loss is irreparable but the memory of his life will always remain an inspiration to all of us who have been associated with him

In connection with our educational activities we are all increasingly aware of the important part which our journal, the Annals of Internal Medicine, continues to play in this field The Annals has continued to grow both from the standpoint of the high character of the scientific contributions to medical literature which it presents and also in the support from subscribers and advertisers which is founded upon a growing appreciation of its value We owe this in no small part to the able and skillful leadership of its editor

* Presidential Address, delivered at the Convocation Exercises of the American College of Physicians, Twentieth Annual Session, Detroit, March 4, 1936

The general financial condition of the College is extremely satisfactory and has been ably directed by our Finance Committee and our treasurer

There are two developments in the affairs of the College which have occurred during the past year, to which it seems timely to call special attention. The first of these is the serious consideration upon the part of our Officers and Regents of the desirability and possibility of acquiring a permanent home for our College. There are many reasons why this seems desirable, and if feasible it will add dignity and assurance of permanency to our organization. That this plan can be even considered is due fundamentally to the soundness of our financial position, and it is not unlikely that in the near future the ownership of our own home may be an assured fact.

The second notable development is the direct outcome of a policy strongly urged by my predecessor in the office of President of the College, Dr. Jonathan C. Meakins. I refer to the leading part which we have taken in the formation of a National Board for the qualification of internists.

A number of the Board of Regents, under the leadership of Dr. Meakins, for several years have been impressed with the need of better standardization for qualifications leading to the designation of experts in the field of internal medicine, and have felt that our College should take the initiative in meeting the problems raised by this need. Consequently, by vote of the Board of Regents and with the approval of the proper authorities of the American Medical Association, a joint Board of Medical Examiners has been organized for this purpose, under the combined auspices of our College and the Section on Medicine of the American Medical Association. This Board is expected to function effectively in the near future, and by establishing suitable criteria for the qualifications necessary for the designation of specialists in the field of internal medicine will do much to raise the standards of our practice, to develop a more adequate recognition of the special field of medicine, and incidentally will, we believe, do much to improve the standards of qualification for membership in the College of Physicians. We are all very much indebted to the very efficient and arduous labors of the special joint Committee which has been struggling with the many ramifications of this plan during the past year under the chairmanship of Dr. Walter L. Bierring.

More General Problems. While of course we have met here on this occasion under the auspices of and directly in the interest of the American College of Physicians, I am not unmindful of the fact that we of the College are merely one representative part of that larger and more important group, namely, the physicians of America. Consequently, I propose upon this occasion to address you upon some of the problems in modern medicine which seem to me to be of importance to the medical profession as a whole, and in the solution of which we of the College ought to play an active rôle.

It is, of course, obvious to all of us that we are living in a period of change, difficult but extremely interesting and affecting all the relationships of our social order, including that of the practice of medicine.

In the midst of the troubled and even anxious thoughts which the unrest about us may create there is some comfort in the recollection that this is not the first period in history in which civilization as a whole and medicine in particular have gone through similar experiences of change, sometimes approaching revolution but always leading eventually to progress. The period in the world's history when civilization as a whole and medicine as a part of that civilization remained stagnant, nearly dead, was that long thousand years known as the Middle Ages. There was no thought of change during that period, no stimulus of new or revolutionary thought, and in medicine the dogmatic dictums of Galen reigned supreme and unchallenged, and medical thought was like a flickering candle barely kept alight in the recesses of the monasteries. The sixteenth century and the Renaissance brought changes, rapid and frequently revolutionary, in all fields of social endeavor, and medicine shared in this reawakening, largely under the influence of more exact knowledge founded on the study of pathological material through autopsy. But in the light of our modern knowledge even this progress was very halting and imperfect. It was not until the early part of the nineteenth century, following the French Revolution and the Napoleonic era, that very great and important contributions to the knowledge of disease were made under the influence of such leaders as Bayle, Laennec and Louis in France, and in the field of pathology particularly by Virchow in Germany. But the really revolutionary period came in the latter part of that century, with the development of our knowledge of the role of bacterial infection in many diseases, with the names of Pasteur and Koch standing out preeminently as leaders in this new field. It is since those days of 1870 to 1880 that the greater part of the fabric of modern medicine has been created, founded upon the increasing knowledge gathered by unceasing laboratory and clinical research, in such astonishing fashion as to be really bewildering albeit inspiring to those of us who have been privileged to live during this epoch.

But our intense interest in all of these developments has required a devotion of time and concentration of effort, which has quite naturally tended to make our profession individualistic in its approach toward medical problems and often oblivious to other important elements in our social fabric because of the very fascination as well as absorbing interest of the new knowledge which has so rapidly and constantly been developed in our own chosen field.

It is not to be wondered at, therefore, that in our habits of mind as well as in our practice we have tended to become individualists.

But during these latter years the practical application of our growing medical knowledge has become increasingly evident to the world at large, and the same principles which guide us in the treatment of our individual patients are recognized to have great significance to the community as a whole. So that one of the most important changes that have occurred is the realization that society as a whole is interested in these problems quite

as much as is the physician, and that the practical solution of them is perhaps even more the concern of the community than of the physician himself. No longer, therefore, is the physician a man apart, a sort of high-priest of mystery giving out his solemn pronouncements dogmatically, unconcerned with explanation of the reasons why, but rather an enlightened and interested public expects and demands a reasonable understanding of what is going on, and also an extension of our activities far beyond the intimate personal relationships between the individual patient and his physician, to those broader fields which we designate as preventive and social medicine.

Thus, the physician, whether he will or no, has been brought out of his cloistered existence into the field of active participation in community movements of great significance, in which he must play a part as leader, educator and guide or else stand adjudged unworthy at the bar of an exacting public opinion.

This changed relationship has brought us face to face with many problems which previous generations have not considered medical at all but which are pressing upon us for solution. It is of some of these that I will briefly speak to you on this occasion.

Changes Due to the Increase of Medical Knowledge Before, however, we consider these outside relationships it is apparent that many changes in medical practice are due to the rapid development of our knowledge in many directions. Some of these may be briefly summarized.

One of these, of great significance, has been emphasized in Professor Cannon's address to us this evening, that is, the development of the physiological approach to many problems, as distinct from the strictly pathological approach which has been the main basis of medical science up to recent years. It appears to be evident that a closer study and appreciation of functional disturbances during life are to take a much larger share in our medical thinking in many fields. This field of study is difficult, and in it we have only made a beginning, but it offers opportunities for further progress which may have great importance and significance.

Then, we note the great progress in our knowledge of chemistry as applied to biology and to medicine. Processes which we have been accustomed to consider as morphological, now appear to have their ultimate basis in microscopic chemistry. Not only in the diseases of metabolism but also in the infectious diseases, where the chemical constituents of pathogenic bacteria together with the character of the tissue reactions which they cause are now being studied, chemistry is becoming increasingly important.

Of course, in the field of the hormones and the vitamins we have seen a rapid development of our knowledge, due to chemical research.

In general, our conceptions of the physical structure of living matter, the chemical changes which accompany vital activities, and our increasing knowledge of chemical substances which may control such activities, are the result of modern research. These researches have also led to a marked advance in the development of pharmaceutical preparations and to definite improvement of numerous therapeutic agents placed at our disposal.

Then we have the fascinating new field of knowledge opened up by the discovery that ultramicroscopic viruses are the causes of some of the important infectious diseases the etiology of which has heretofore baffled us during the bacteriological era. These researches open up new fields of knowledge and give promise of better control and treatment of these diseases.

One of our great problems is to keep abreast of all this new knowledge, so that we and our patients may receive the maximum benefit from it. We must continue to be students as well as practitioners, and there is always real danger that our practice may lag behind the advance of medical knowledge.

Changes Due to the Application of the New Knowledge It is here that we move out from our narrower, strictly professional sphere into our contacts with the community.

Specialism One of the first of these changes has been due to the very amount of new knowledge which has made it impracticable, even impossible, for any one mind to grasp all of the ramifications of this new knowledge and to make the best use of it.

It is this fact, I think, rather than any economic motives, that has led to the development of specialism in medicine.

No one who has grown up in the medical profession can fail to have the highest respect and the deepest affection for those representatives of our profession who have carried on against the greatest difficulties with courage and devotion and who have been not only the physician but also the wise counselor and friend of the families entrusted to their care. All honor always to the general practitioner!

It is obvious, however, to them as well as to the rest of us, that if the highest attainment of skill and knowledge is to be at the disposal of the community, many of us must devote our special attention to certain specific lines of study and of practice. In losing some of the personal touch of the family physician there has nevertheless been great gain in the development of better diagnosis and treatment. How to hold the advantages of each of these groups and to have them go on together to their mutual advantages and particularly to the advantage of our patients, is one of our modern problems.

I feel that we are taking an important step forward toward the solution of this problem in the plans which have been formulated for the application of standards by which specialists in internal medicine may be recognized, and it is particularly to be noted that in this plan special emphasis is placed upon the essential importance of an adequate preliminary training in general medicine as the foundation of any specialty.

The defects in the practice of the specialties would appear to revolve mainly around the temptations to their abuse through false or misleading claims of special proficiency, through the multiplication of unessential and costly procedures or through inequitable professional charges, in a word they are due to the commercialization of the public demand for expert serv-

as much as is the physician, and that the practical solution of them is perhaps even more the concern of the community than of the physician himself. No longer, therefore, is the physician a man apart, a sort of high-priest of mystery giving out his solemn pronouncements dogmatically, unconcerned with explanation of the reasons why, but rather an enlightened and interested public expects and demands a reasonable understanding of what is going on, and also an extension of our activities far beyond the intimate personal relationships between the individual patient and his physician, to those broader fields which we designate as preventive and social medicine.

Thus, the physician, whether he will or no, has been brought out of his cloistered existence into the field of active participation in community movements of great significance, in which he must play a part as leader, educator and guide or else stand adjudged unworthy at the bar of an exacting public opinion.

This changed relationship has brought us face to face with many problems which previous generations have not considered medical at all but which are pressing upon us for solution. It is of some of these that I will briefly speak to you on this occasion.

Changes Due to the Increase of Medical Knowledge Before, however, we consider these outside relationships it is apparent that many changes in medical practice are due to the rapid development of our knowledge in many directions. Some of these may be briefly summarized.

One of these, of great significance, has been emphasized in Professor Cannon's address to us this evening, that is, the development of the physiological approach to many problems, as distinct from the strictly pathological approach which has been the main basis of medical science up to recent years. It appears to be evident that a closer study and appreciation of functional disturbances during life are to take a much larger share in our medical thinking in many fields. This field of study is difficult, and in it we have only made a beginning, but it offers opportunities for further progress which may have great importance and significance.

Then, we note the great progress in our knowledge of chemistry as applied to biology and to medicine. Processes which we have been accustomed to consider as morphological, now appear to have their ultimate basis in microscopic chemistry. Not only in the diseases of metabolism but also in the infectious diseases, where the chemical constituents of pathogenic bacteria together with the character of the tissue reactions which they cause are now being studied, chemistry is becoming increasingly important.

Of course, in the field of the hormones and the vitamins we have seen a rapid development of our knowledge, due to chemical research.

In general, our conceptions of the physical structure of living matter, the chemical changes which accompany vital activities, and our increasing knowledge of chemical substances which may control such activities, are the result of modern research. These researches have also led to a marked advance in the development of pharmaceutical preparations and to definite improvement of numerous therapeutic agents placed at our disposal.

Then we have the fascinating new field of knowledge opened up by the discovery that ultramicroscopic viruses are the causes of some of the important infectious diseases the etiology of which has heretofore baffled us during the bacteriological era. These researches open up new fields of knowledge and give promise of better control and treatment of these diseases.

One of our great problems is to keep abreast of all this new knowledge, so that we and our patients may receive the maximum benefit from it. We must continue to be students as well as practitioners, and there is always real danger that our practice may lag behind the advance of medical knowledge.

Changes Due to the Application of the New Knowledge It is here that we move out from our narrower, strictly professional sphere into our contacts with the community.

Specialism One of the first of these changes has been due to the very amount of new knowledge which has made it impracticable, even impossible, for any one mind to grasp all of the ramifications of this new knowledge and to make the best use of it.

It is this fact, I think, rather than any economic motives, that has led to the development of specialism in medicine.

No one who has grown up in the medical profession can fail to have the highest respect and the deepest affection for those representatives of our profession who have carried on against the greatest difficulties with courage and devotion and who have been not only the physician but also the wise counselor and friend of the families entrusted to their care. All honor always to the general practitioner!

It is obvious, however, to them as well as to the rest of us, that if the highest attainment of skill and knowledge is to be at the disposal of the community, many of us must devote our special attention to certain specific lines of study and of practice. In losing some of the personal touch of the family physician there has nevertheless been great gain in the development of better diagnosis and treatment. How to hold the advantages of each of these groups and to have them go on together to their mutual advantages and particularly to the advantage of our patients, is one of our modern problems.

I feel that we are taking an important step forward toward the solution of this problem in the plans which have been formulated for the application of standards by which specialists in internal medicine may be recognized, and it is particularly to be noted that in this plan special emphasis is placed upon the essential importance of an adequate preliminary training in general medicine, as the foundation of any specialty.

The defects in the practice of the specialties would appear to revolve mainly around the temptations to their abuse through false or misleading claims of special proficiency, through the multiplication of unessential and costly procedures, or through inequitable professional charges, in a word they are due to the commercialization of the public demand for expert serv-

ice Surely, we as a profession should be able to control and to remedy these evils

Preventive Medicine Perhaps the greatest change which our new knowledge has brought to us is the widening of our sphere of responsibility from the care of the individual patient to that of the community of which this patient is a part This is particularly true, of course, in the field of infectious diseases where the protection of others is quite as important as the cure of the individual patient There are, however, applications of this principle other than that of preventing the spread of infection

Thus we have the developing field of responsibility for large groups of individuals who are not apparently ill Great progress has been made in the survey of such groups through the operation of medical services for industry, for life insurance and for schools, and also through the movement to educate individuals to the importance and advantage of periodic health examinations at the hands of their own physicians

The results of such surveys have already uncovered a large number of unsuspected cases of disease in incipient and remedial stages But this progress has largely been due to the operation of organized groups associated either with governmental or with industrial agencies The individual practising physician has taken too little share in this movement, due largely to faulty training which centers our interest upon obvious disease and has failed to develop a technic and interest in the recognition of slight deviations from the normal which have not yet led to symptoms or complaints on the part of the patient Not only has the bulk of the population not been educated to the point where the average man would consult a physician for a regular check-up once or twice a year, just as he would his dentist, but also the few who do often have their enthusiasm dampened by the lack of interested response on the part of the physicians whom they may consult This whole field demands a different outlook both in our medical education and in our medical practice

Then we have the whole field of prophylactic and preventive inoculations, best exemplified by their use in smallpox and diphtheria but also applicable to other diseases There is also the large field of remedial physical defects found especially in childhood, such as defective teeth, tonsils, adenoids, eyesight, faulty nutrition and the like These conditions in themselves do not constitute disease but are the underlying and predisposing causes of many diseases

We have left this field of service very largely to our public-health and school authorities, excepting in so far as the pediatricians take part in it As a group the pediatricians may be fairly characterized as the best exponents in our profession today of the highest type of general practice combined with an appreciation of the responsibility for preventive medicine But we should not leave this field entirely to our public-health authorities and to our pediatricians

Very recently a new potential force of great significance has been added

to the public-health movement. I refer to the provisions of the Federal Economic Security Act which will make available nearly twenty million dollars a year to be expended through the Public Health Service and the Children's Bureau.

Serious problems are here involved. In what directions are these funds to be expended, how will their administration be affected by political considerations, what properly trained personnel is available, and how will these new activities be related to those of the medical profession?

These great appropriations signify enormous possibilities for improving the health of the nation, but they also constitute a new opportunity and a challenge to the medical profession.

In the first place, in these days of professional insecurity an attractive field of service is opened up to many physicians. I must confess that were I at the present time in the stage of my medical career which I was passing through when five or ten years out of the hospital, this prospect for public-health service would have a great appeal to me. I hope that there will be many of our younger best trained physicians who may become enlisted in this public-health service.

In the second place, however, we must realize that this new development will greatly strengthen the organization of our health authorities and might easily lead to an increase of the amount of public or state medicine. Dr. Thomas Parran, Jr., the Commissioner of Health of the State of New York who undoubtedly will have a considerable influence in the formation of these new policies, hopes that it will "liberalize present medical practice, coordinating it with public-health and medical services." He would propose "to assist the private physician by providing for him laboratory, hospital, nursing and other facilities for the treatment of his cases, and at the same time relieve part of the load of catastrophic illness from the low-income group."

In this or some similar manner we as physicians must cooperate in this movement or face the possibility of the slow advance of State medicine.

What a wonderful power we, as a body, could exert in this field if we each individually constituted ourselves health officers for the families under our care, detecting and correcting defects, following up sources of infection in syphilis, in diphtheria and other infectious diseases, checking the contacts in our cases of tuberculosis, and in general in every way cooperating closely with our health officials in their efforts to prevent disease! This is the challenge of preventive medicine to us. We must either take our proper place in this field or we will surely be pushed aside.

Mental and Emotional Problems. There is another field perhaps even less well understood and possibly more important than those we have been considering. I refer to those influences of our modern life which affect the behavior and the mental, nervous and ethical reactions of individuals.

There can be no doubt that the tremendous incidence of various forms of insanity, of mental deficiency as well as of functional nervous disorders

is susceptible of decrease by preventive measures, and for the prevention of these conditions the medical profession must take considerable responsibility.

The role of syphilis in the causation of many forms of mental and nervous disease is known. But even here we are doing comparatively little to apply well established principles of treatment. When we come to other disorders of which the causes are less definite, as for example, faulty inheritance, faults of early childhood environment or education, or the pressure of modern social, business and industrial life how little are we, as advisers, doing to influence either the environment in which we all live or the individual habits of the patients under our care!

Perhaps the lack of intimate personal contact which we have lost in the passing of the family physician is a factor in the situation. But whatever may be the explanation, is it not true that we, as physicians, under the influence of our passion for modern and exact science have lost sight of those more intangible and less demonstrable factors which we call the nervous and the psychic? Not only in the prevention of actual nervous or mental disorders is this factor important but also in the treatment of our patients suffering from any disease, particularly the chronic disorders. A better recognition of the importance of their mental processes would appear to be demanded which would bring us back to a fundamental appreciation of our patients as individuals rather than as cases of disease, and to an understanding of their personalities and the influences under which those personalities have developed and are manifested. Is it not at least partly true that the extraordinary development of cults of faith and mental healing in this country, estimated to affect approximately ten millions of our people directly or indirectly, may be attributed to a lack of interest in and appreciation of these factors by the practising medical profession? Personally I have a very strong feeling that as a whole we of the profession are constantly losing magnificent opportunities not only to help our patients get well but also to control and develop their characters and personalities as evidenced by their nervous and emotional as well as their intellectual responses. In other words, have we not been affected too much by materialistic and scientific progress and failed too often to appreciate the importance of the individual as a whole, which would include all of these psychic, emotional and ethical values in his life as well as the physical?

Biological Aspects Our consideration of certain aspects of preventive medicine has emphasized particularly the prevention of disease and the saving of human life. As far as the general population is concerned this means that we have been attempting to diminish subtractions only. But what about the additions? I refer to the control of increase of population. Have we physicians any responsibility for this?

This is perhaps a somewhat new slant on community responsibility to most of us. The problem, however, is with us. In certain centers the pressure of overcrowding and overpopulation is acute, and in times of economic depression the effect not only upon comfort and happiness but

also upon health and life itself is very real. Students of biology are becoming very much interested in this problem. It is, of course, a part of the general field of eugenics which is concerned not only with the quantity but also with the quality of the population.

At the present time, where this problem concretely confronts the physician is in the question of limitation of births, as involved in contraception and in the interruption of pregnancy. It is not my purpose to deal exhaustively with this highly disputatious subject. But I simply wish to lay before each of you some thoughts for your individual consideration.

Many of us certainly cannot accept the doctrine which sacrifices the threatened life of the mother for the potential existence of the infant. But I wish to raise in your minds the searching individual question whether our modern tendency to exercise our opportunities for advice concerning contraception and the interruption of pregnancy has not been gradually and increasingly influenced by personal and economic considerations, whether, in other words, we are not becoming gradually calloused to a lack of appreciation of the value of human life as such, and whether, particularly in our large cities under the pressure of economic conditions, we are not imperceptibly laying ourselves open to the criticism from certain religious quarters that we are unjustifiably and unethically interfering with natural processes?

I further wish to raise the question in your minds as to whether our approval of contraception in general has not imperceptibly led to a change in our attitude toward the ethics of the other problem, that of early abortion, and as to whether this, if true, is not having its influence upon our conception of the sanctity of human life in itself and consequently upon our attitude toward family life in general as the basis of our society? In other words, are not some of our critics at least somewhat in the right in suggesting that tendencies in this direction might lead us ultimately in the direction already followed in Soviet Russia?

Another aspect of this same problem is raised by the recent discussion concerning the ethics of euthanasia. I think that there is little doubt that we are all pretty much in agreement on this subject, but I again raise the question as to whether the support of euthanasia in some quarters and the interest which the public discussion of it has aroused are not again indications that there is an imperceptibly changing point of view toward the sanctity of human life?

Social and Economic Problems of Organized Medicine Perhaps the greatest recent changes of all in our medical relations have been those which involve the social and economic order. According to the recent trend these relationships also involve important political ramifications, so that we find ourselves as a profession brought face to face with many problems which have not particularly concerned our forefathers in medicine. Important questions of serious moment have been raised, and we cannot escape some consideration of them, much as we might prefer to devote our time and energies to more strictly medical problems.

The recent widespread interest in these problems was probably crystallized about the reports of the Committee on the Costs of Medical Care. After several years of very extensive study this Committee brought out reports which, while they contained many data of interest and value, led to a division of interpretation among the members of the Committee itself and have precipitated a widespread and sometimes acrimonious discussion among the medical profession and the community at large.

I think that any fair-minded person who has studied these reports will appreciate that they reveal conditions heretofore incompletely recognized and understood, which demand serious consideration and, if possible, remedy. The most important of these perhaps are those which relate to the unequal distribution of the burden of sickness, the unequal and often inadequate compensation to physicians, the unequal and inadequate provision of medical services in many communities, and the disproportionate cost of notoriously ineffective instruments of treatment such as proprietary and patent medicines as compared with the cost of adequate medical and hospital service.

All of us who practice medicine are well aware that long illness is a great burden, often a crushing one, upon our patients, and we have long been accustomed to adjust our own services and their cost to existing circumstances. All fair laymen recognize the fact that, as a profession, our aim and ideal has been the provision of services rather than insistence upon adequate financial compensation. That there are exceptions to this rule also, we of course all well know. But in our hearts we are assured that we cannot in fairness allow the motives of our profession as a whole to be impeached.

The consciousness of this fact should not lead us, however, to contend that because in general we know that our motives have been generous and fair, consequently all is well and no changes are desirable or necessary. It is very probably true that with the improvement in general social conditions in the United States there has also been an accompanying improvement in the character of medical service, and very likely, as has been claimed, no country in the world enjoys better medical service than ours.

But this is far from sufficient. The very progress that we have made is an incentive and challenge to further improvement, and it would appear from recent studies and analyses of the situation as it affects medical practice in this country that the need for such improvement does exist, and we are all individually conscious of that fact. Consequently it would appear to be a great mistake for us as a profession, either individually or as an organized body, to resist as unnecessary and unfair the demands for a study of this situation and for the application of appropriate remedies when and if they are found necessary. It is very gratifying to know that the recent trend in organized medicine is away from a general denial of such need and is turning toward a more rational study of the situation and a willingness to cooperate in making reasonable changes.

Quite properly however, we as a profession insist that the problems of medical care are better understood by the medical profession than by other groups. Without in any way denying that the community as a whole, the members of which, when sick, constitute the patients under our care, is directly and primarily interested in these problems, nevertheless we feel that by our experience and training we are the ones best qualified to understand the various ramifications of this problem and to take the leadership in applying effective remedies. This can only be done, however, if, as individuals and as a body, we approach this problem with the same open mind and scientific spirit with which we would approach a more strictly medical problem.

Already considerable progress is being made in this direction. In the past few years a very large number of experimental activities looking toward a more equitable distribution of the cost of illness and remuneration of physicians have been instituted under medical auspices. The results of these experiments are varied and as yet inconclusive, but it is evident that progress is being made. It appears that quite independently of the financial and economic factors involved, our chief concern as physicians should be that high standards of professional service be maintained and that any proposed change should improve rather than impair these standards.

The immediate burning question, about which considerable discussion and debate have already occurred, is that of health insurance. This method of meeting the problem has been generally adopted in the countries of Europe. Studies of the operation of these systems have led to conflicting reports as to their results. But from the discussion, I think, has come a realization that there are many defects in existing health insurance systems and that, taken all in all, with the conditions as they exist in the United States the adoption of compulsory health insurance, as organized in England and Germany or even in Denmark where it has been most successful, would be an unwise experiment for this country. It is, therefore, I think, a matter on which we are to be congratulated that plans to include health insurance in the National Economic Security Bill were laid aside by the present Federal Administration. This result was due very largely to the arguments raised by members of our profession, and in so far as this change in the proposed plan was due to medical opposition, it places upon the organized profession an increased obligation to make every effort to solve the problems involved by other means which may give the good results sought by compulsory health insurance, without incurring the objections and dangers which it entails.

It is estimated that there are at least sixty types of experiments now going on in various communities of this country along these lines at the present time. Some of them are already obvious failures, others are apparently fairly successful. All of them appear to have some defects. Under a broad-minded leadership our profession should be in a position to analyze

and assess the value of these experiments. Such a study will take time and money as well as special ability. In view of the great service it might be to the cause of public health and general welfare in which the Foundations are interested I very much hope that they may join with organized medicine in a cooperative analysis of these important experiments. Such enlistment in a common cause might also serve to bring closer contact between the great health Foundations and the organized medical profession. In recent years there has been an unfortunate tendency for them to be arraigned in opposite camps. Now, it so happens that I know the leaders of these social groups very well. They are a fine lot, quite as fine in their way as we are in ours, and, I may add, they also have similar failings as well as similar virtues, in other words they, too, are human.

The interests of these Foundations and of the medical profession are in the long run the same, and they can only be best served if the representatives of each work shoulder to shoulder to solve these important problems, without any self-seeking motives and particularly without bitterness and jealousy. Evidence that this most desirable state of affairs is gradually coming about is now appearing, and I feel more confident than at any other time during the past few years that wise and equitable solution of this problem will eventually be evolved.

Medical Personnel One phase of the problem, for which the medical profession is largely if not exclusively responsible, is the question of the amount and caliber of medical service which is available. As to quantity, this goes back to the number of physicians, and in these days when the path of least resistance leads the youth of our country to further study rather than an attempt to get a job, our medical schools are flooded with applications, the number of graduates in medicine has increased and the saturation point of numbers has already been reached in many of our communities.

Judging by the low average rate of income of physicians and the struggle of the younger members of the profession in our large cities, one suspects that either there are too many physicians or else that their distribution is faulty. That the latter is true in many communities of our country has been demonstrated. It would therefore appear to be our first responsibility to take the lead in supplying better distribution of service where needed, and then, on the other hand, to bring pressure to bear upon our medical schools to restrict the number of graduates to the need, while at the same time improving their quality, by which we mean higher standards of ethics and ideals quite as much as improved intellectual proficiency and professional training.

The representatives of our best medical schools are well aware of these problems and are giving serious thought to the responsibilities which devolve upon them. It is not too much to hope that they will be able to meet this phase of the situation adequately.

Hospital and Dispensary Abuse Another burning question in our large

cities is what has been termed hospital and dispensary abuse, by which we mean that these institutions which owe their efficiency mainly to our voluntary and unremunerated medical service, are patronized by many who economically are in a position to pay for private medical service, thus putting the physicians in a position of serving in the hospitals and dispensaries against their own economic interests

Quite properly the representatives of organized medicine are insisting that safeguards against this abuse be thrown about the hospitals and dispensaries, and progress is being made in this direction. They are, however, making other recommendations of more dubious propriety, in my opinion. I refer particularly to the suggestion that all physicians in hospitals and dispensaries should be paid for the medical services rendered. If this were done, we would in the first place put an overwhelming increased financial load upon the administrative expense of these institutions. In the second place we would be demanding as physicians compensation for services which it has always been our pride and boast that we have given freely. A great deal of the criticism of the medical profession of recent years has been counteracted by the appreciation of the high-minded, generous contribution of service to the sick poor which we have always made. It would appear to be a great pity to take away this privilege as well as strategic advantage from our profession. Moreover, all of us in this body appreciate the fact that our postgraduate education depends upon our hospital practice and that we are only too happy to do this work because of the opportunities for improving our medical competency and the joy that we have in the acquisition of new knowledge.

Another phase of the subject which we cannot afford to overlook is that the placing of all of the staff of our State and municipal hospitals upon a salary would tend to make these positions more political and create a real danger that in this very plan so strongly recommended in some medical quarters we would be taking the first step toward that anathema of organized medicine, namely, State medicine.

That there exist, however, many instances in which hospital or dispensary practice infringes on the rights and privileges of individual physicians, there appears to be little doubt. Changes in the existing order may be desirable, but we, as physicians, are interested both in the institutions and in the individuals, and we should make sure that any such changes are mutually fair and beneficial to both parties.

Socialized or State Medicine This leads us finally to the consideration of socialized or State medicine as a present-day problem in medical economics.

In the first place, I think, we must recognize the fact that we already have a considerable amount of State medicine in this country, with the apparent approval of the medical profession. We see it in the State care of the insane, of the mentally defective and of the tuberculous, we see it in the Army and Navy medical service, we see it in many of the activities in the

field of preventive medicine under the control of the public departments of health, and I have already discussed the possibility of its extension under the Social Security Act.

During the depression we have also seen a very insidious extension of State supervision of medical service in the administration of medical care for those on home relief. In some communities this is very wisely and properly administered with the cooperation of organized medicine through the county societies. But medical safeguards are often objectionable to administrative authorities, and there are not a few who are in favor of paying straight salaries for physicians engaged by the State for this medical service. Properly organized, controlled and supervised, this very need for home medical relief which our present economic distress has brought out can be utilized for the improvement of medical service from both the curative and the preventive aspects. In some communities this is being done, high standards of medical practice have been set up and insisted upon to the mutual advantage of the sick poor and of the physician. Where medical control of this service, however, is replaced by purely administrative or political control, the danger is great that medical standards will be lowered and the opportunities for progress not only lost, but actual deterioration of the present standards of service may result. This is of course exactly what we fear in what is called State medicine, and the fears are well-grounded.

Not only have we seen tendencies leading toward a mechanical and superficial character of medical service in medical home relief under State auspices but also in the operation of the workmen's compensation laws in many States we have had a very instructive illustration of the demoralization of standards which is always likely under a system of medical service under political control. Some of these workmen's compensation evils are being corrected in some communities, but only when active and wide-awake members of the medical profession have been alive to the situation and have taken an active part in remedying the abuses and eliminating faulty methods.

Not the least important responsibility of the medical profession in this field of economics is the insistence upon high ethical standards as distinct from merely high standards of medical proficiency. We are all of us aware of the insidious infiltration of our standards of professional probity which has been brought out under the stress of the economic depression. There has recently been published a sordid story of the practice of medicine at its worst. The author of this book evidently speaks from first-hand knowledge, and the allegations made are sufficiently plausible to bear the stamp of actual experience leading us through many sordid details into the haven of socialized State medicine as the remedy. This would appear to be an extraordinary deduction, but at the same time this line of argument probably represents the opinion of a considerable number of people both within and without our profession, and consequently cannot be entirely disregarded.

In the first place it is obvious that the experience of this physician was

very unfortunate and represents a very small fraction of the profession. We would like to know a little more of the professional company which the author kept before he became a convert to the doctrine of State medicine, and would particularly like to know whether there are no ways and means available of correcting these abuses by bringing those guilty of them out into the open on charges of unprofessional conduct. I am convinced that if we could simply expose these instances of unethical conduct they would quickly defeat themselves, but we as a profession have been perhaps too complacent in regard to them and too negligent of active efforts to eradicate them. On the other hand, if the undesirable elements of our profession are not eliminated, a system of State medicine would be apt to find these very individuals in control of such a system and much more powerful and dangerous than they are at present. We need to clean house of these elements and at the same time to control the situation at the source, namely, in a more rigid selection of those admitted to our medical schools and to medical practice.

CONCLUSIONS

I feel that we have wandered considerably afield in our discussion of the changing order in medicine.

The main thought which I have wished to emphasize is that there exists a pressing necessity for the medical profession to adapt itself to modern changing conditions.

We ourselves are mainly responsible for putting our house in order, and if it is in order we need have no fear that it will be sold over our heads either to irregular cults, to socialism, to the State, or to anyone else.

Our chief objective must always be to develop the art and science of medicine. But without sacrificing this main objective we must widen our interests to include those of the community as a whole. As we move out of our cloistered life of concentrated interest in our own special and fascinating job into the larger field of more general human interests we have the opportunity for a greater service which will be less individualistic and more social-minded. Thus will our horizon be immeasurably widened and we ourselves may at the same time become better physicians and better citizens.

God forbid that we should wrap ourselves about in the cloak of self-satisfaction, content with our own immediate objectives and past achievements, or that, on the other hand, we should assume an attitude of aggressive trade unionism, intolerant of criticism, resistant to change and insistent upon our own special privileges and interests to the exclusion of those of others!

As individuals and as a profession we need to take thought of these matters and then move on to meet the challenge in a manner worthy of the fundamental principles and the high ideals upon which our profession is founded.

Without presuming to present any specific program of action the prin-

ciples upon which such action should be based might be formulated as follows

1 A strict adherence to Truth both as we now know it and as it may be developed in the future by continued persistent research into the as yet hidden secrets of Nature

2 An absolute ethical Honesty Honesty in our thinking as well as in our professional conduct

3 A devotion to the spirit of Service Service not merely to those individuals entrusted to our care but to the whole community

May we ever be able truthfully to claim for our profession that our inspiration is the opportunity for service, not the hope of reward!

LYMPHOPOIESIS, LYMPHATIC HYPERPLASIA, AND LYMPHEMIA FUNDAMENTAL OBSERVATIONS CONCERNING THE PATHOLOGIC PHYSIOLOGY AND INTERRELATIONSHIPS OF LYMPHATIC LEUKEMIA, LEUKOSARCOMA AND LYMPHOSARCOMA^{*}

By B K WISEMAN, M D , *Columbus, Ohio*

TABLE OF CONTENTS

The Physiology of Lymphopoiesis
The Pathology of Lymphopoiesis in Non-Infectious States
Chronic Lymphatic Leukemia
Lymphatic Pseudoleukemia
Leukosarcoma
Lymphosarcoma
Aleukocytemic Lymphatic Leukemia
Discussion
Conclusions

It is doubtful whether there is any group of diseases about which there is more controversy over the clinical classification pathogenesis and morbid physiology, than those which primarily involve the lymphatic tissues. As contrasted with those dyscrasias which have their origin in the sister blood forming tissue, the bone marrow, the greater difficulty in the interpretation of morbid processes in the lymphadenopathies is quite manifest. Thus, while the division of the diseases affecting the bone marrow into various categories is unanimously agreed upon and the principal features of their pathologic-physiology are accepted with little dissension, the mechanism and meaning of pathologic alteration in the lymphatic tissues remain today almost as obscure and chaotic as for the past fifty years. Witness, for example, the popular use of the terms lymphoblastoma and lymphoma, designed to encompass most of the non-infectious lymphadenopathies. The continuance of the use of such vague general terms is an admission of the confusion that prevails in this field.

The reasons for the difficulties that have continued to beset workers in this field are not difficult to find. They are largely, if not entirely, the obstacles that attend the interpretation of the histogenesis of the lymphocyte. No completely satisfactory concept of the identity, life history, and specific functional potentialities of the lymphocyte has yet been accepted. The fundamental cytological studies of Sabin and her associates have gone farthest perhaps toward establishing this cell in its proper relationship to the other cells of the blood forming tissues,¹ and are basic to any interpretation of the rôle of this cell in the lymphatic dyscrasias.

^{*} Read in part May 1 1935 at the 19th Annual Meeting of the American College of Physicians, Philadelphia, Pa., under the title "The Fundamental Mechanism in the Production of Chronic Lymphatic Leukemia."

From the Department of Medical and Surgical Research, Ohio State University, Columbus, Ohio

The problem of chronic lymphatic leukemia is essentially the problem of the pathologic-physiology of lymphopoiesis. Any rational attempt to trace the course of events in which the lymphocyte plays the dominant rôle must take into consideration the well established facts relating to the known pathologic alterations in which this cell type is the chief reacting unit, and also must be consistent with the physiologic conditions under which this cell reproduces itself. Further, it is clear that the unsatisfactory state of our understanding of both the physiology and the pathology of lymphopoiesis directly reflects the uncertainty and conflicting opinions that prevail with regard to the lymphemic states. Admitting, then, that any discussion concerning the mechanism of chronic lymphatic leukemia is hampered by our incomplete knowledge of this subject, it is desirable, nevertheless, if only for the purpose of stimulating new lines of thought and research, to review critically the available facts and to add certain original data bearing upon the problem. Such an analysis has formed the basis for the present concept which suggests a rational explanation of this enigma on the basis of our present state of knowledge.

THE PHYSIOLOGY OF LYMPHOPOIESIS

Reference to chart 1 shows schematically the course of events in the evolution of the lymphocyte from the mesenchymal rest, the non-phagocytic reticulum cell, through the phases of maturation to the definitive small round cell readily identified wherever found as the lymphocyte. While it is believed that all of the primitive cells (including the reticulum cells) are totipotent, yet because of the environmental conditions, the conditioning stimuli received, or both, these precursors mature only in the direction of lymphoblasts in lymph nodes and spleen and in a few other locations. All cells below level 2 are fully differentiated units and appear to have lost their power to reproduce cells other than lymphocytes. As indicated by the chart, lymphopoiesis is usually effected by progressive stages of maturation and division (chiefly mitotic) through the successive levels 1, 2, and 3, the latter level being most active (quantitatively) under physiologic and certain pathologic conditions. However, lymphopoiesis may also be effected to an important degree by a rapid division of cells in level 4 (chiefly amitotic). The qualitative characteristics of these cell types have been described previously in detail - ³

The significance of the histologic structure of the lymph nodes in which these changes take place has long been a subject of controversy. The pioneer hypothesis of Flemming ⁴ which emphasized the significance of the so-called germinal center, though contested by Marchand, ⁵ Hellmann, ⁶ Heilmann, ⁷ Latta, ⁸ Heiberg, ⁹ Pol, ¹⁰ and many others, has been vigorously supported by the work of Aschoff, ¹¹ Groll and Krampf, ¹² Maximow, ¹³ et al. At present the prevailing opinion supports Flemming's original concept of the import of the secondary nodule. Original work in this laboratory has indicated

LYMPHOPOIESIS

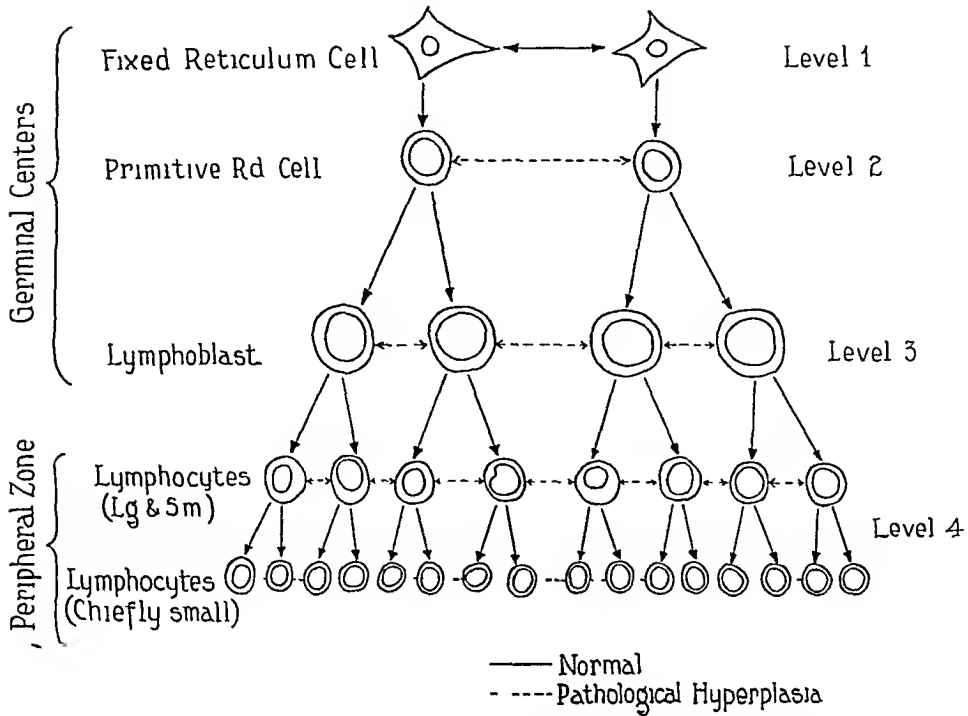


CHART 1 A graphic representation of physiologic and pathologic lymphopoiesis. The cells, in their relationships to normal physiologic lymphocyte production, are shown by connecting them with solid lines. The non-phagocytic reticulum cell gives rise on the one hand to daughter reticulum cells and on the other, by maturative phases, to primitive round cells and thence to lymphoblastic units. Further division and maturation of the latter elements result in the production of the mature cells of the peripheral zone, which not only encircle the germinal centers but also are diffusely distributed throughout the lymph node. Normally most of the proliferation occurs by concomitant maturation and division. However, in the pathologic states of leukemia and lymphosarcoma, it is suggested that division is accentuated and maturation is limited. Various degrees of maturative arrest result in production of the cells of various levels of immaturity as seen in different cases of these diseases. This is indicated by the horizontal dotted connecting lines indicating proliferation with minimal maturation. It is clear from this chart that, theoretically, pathologic proliferation with maturation arrest may be either neoplastic in nature, or metabolic in the sense that unknown disturbed physiologic factors permit or cause undue proliferation without concomitant maturation.

that intense stimulation of the formation of lymphocytes results in a proliferation of the germinal center tissue which breaks through the limiting zone of small lymphocytes and may eventually almost completely fill the entire node within the capsular borders. As this tissue extends through the node it becomes mixed more and more with cells of level 4, so that its identity becomes less and less clearly defined, until in the completely hyperplastic node the entire content of the structure reveals only a diffuse lymphatic tissue with a thorough mixing of all the various types of lymphocytes. Lymph nodes with small but prominent germinal centers are probably resting structures. This would account for the histologic differences between the peripheral deposits of lymphatic tissue which contribute only slightly to the

mass of circulating lymphocytes and those deposits about the gastrointestinal tract which are continually being stimulated by afferent streams from the gut and which, by their efferent vessels, supply nearly all the blood lymphocytes^{14, 16}

Chart 1 shows that when normal maturation and division both occur, lymphopoiesis is expressed histologically by the prominence and extension of the tissue represented in levels 1, 2, and 3, i.e., by the germinal center tissue of Flemming. It indicates, however, that abnormal proliferation is theoretically also possible by specific multiplication without maturation of the cells at any of the levels shown, since all of these cells have the power to reproduce themselves. It is further evident that neoplastic changes may occur at any of the stated levels and thus provide a third mechanism for the over-production of lymphocytes. Each of these three mechanisms may conceivably give rise to pathologic states characterized by proliferative phenomena. The significance of these potentialities will become clear in the later discussion of certain of these pathologic states.

A study of the blood and tissue changes occurring in infectious mononucleosis serves to emphasize the orderly course of events which occurs when the stimulus to increased production of lymphocytes as provided by this infection is pronounced. Chart 2 records the significant hematologic observations made upon patient H. W. from the time he came under observation (24 hours after the onset of the disease) until the blood findings returned to normal. The lymphocytes, polymorphonuclear leukocytes and monocytes, classified by the supravital technic, are shown in absolute numbers together with the totals for white and red cells. In the lower block are plotted the values in per cent for the young lymphocytes as determined in Wright-Giemsa stained blood films, classification being made according to the principles outlined in an earlier publication.² It will be observed from a study of this chart that whenever the total lymphocytes exceed the normal number for an individual in health, the percentage of young types is distinctly above the upper limit of normal (over 10 per cent). It is also clear that as the total number of lymphocytes in the peripheral blood fluctuates, there is a corresponding and parallel fluctuation in the percentage of young forms. This is shown especially well during the repeated observations made on Dec 5, when a study of the blood was made every 15 minutes for three hours. These facts indicate that delivery of increased numbers of lymphocytes to the blood is attended by an increasingly marked shift to the left in this series of cells and bespeak the origin of the cells from a series of maturative phases involving the increased activity of germinal centers, as indicated in chart 1 for levels 3 and 4.

Further evidence for this belief is secured by an examination of the pathological tissue in cases of infectious mononucleosis. A cervical node was obtained Dec 6 by biopsy from a patient, C. W. Z., early in the course of the disease. The photomicrographs (figures 1 and 2 in plate 1) show quite plainly the proliferating germinal center tissue infiltrating the

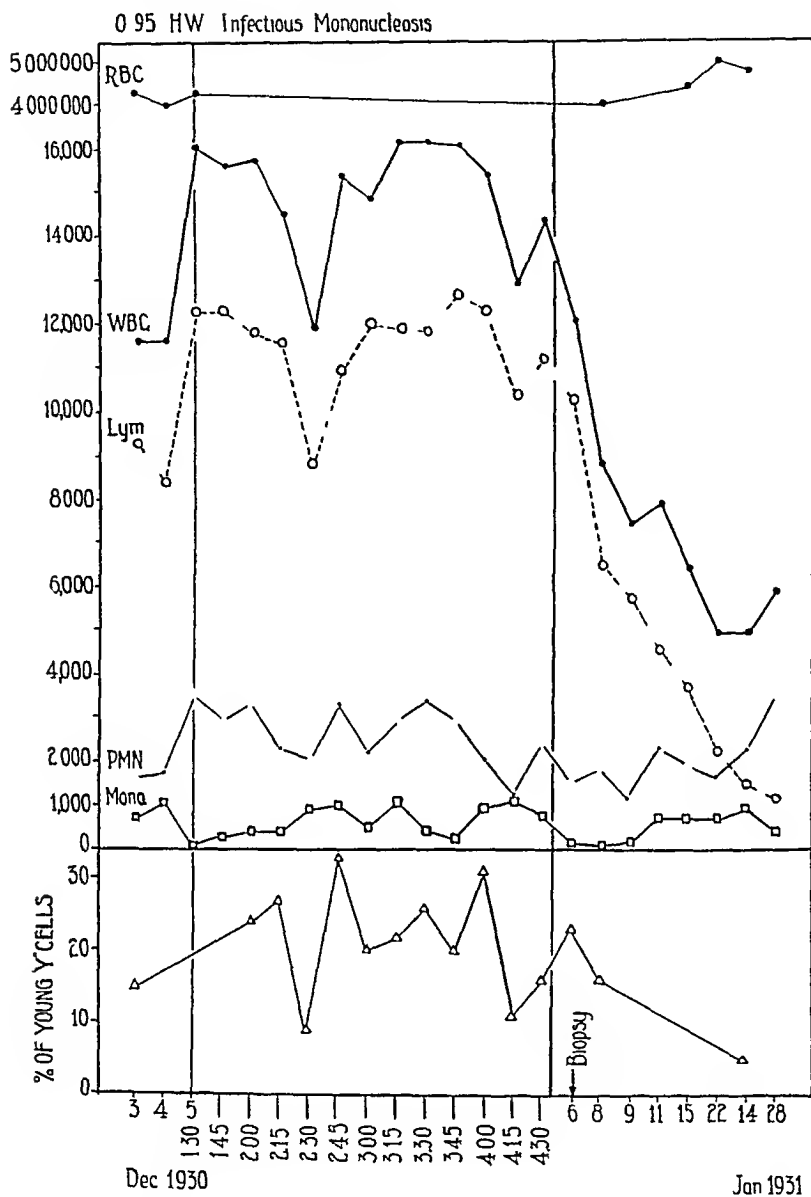


CHART 2 Blood findings obtained by study of case H W who had infectious mononucleosis. Serial 15 minute counts were made during the period indicated on Dec 5, 1930 and the percentage of young lymphocytes charted to contrast with the fluctuation in total numbers of lymphocytes. The correlation between increase in young cells and increase in total numbers is evidence that lymphopoiesis is physiologic as described on chart 1. Tissues from this case shown on plate 1, figures 3 and 4.

entire gland to such an extent that the greater portion of the node is composed of pre-lymphoblastic units, indicating that the supply of lymphocytes is obtained by increased activity and functioning volume of the germinal center tissue of Flemming. The lymph node from patient H W was removed late in the course of the disease, just prior to the restoration of the lymphocytes to normal levels (chart 2). The microscopic character of the

tissues is now totally different (figures 3 and 4 in plate 1). The sections clearly show that "pure" germinal center tissue is much less obvious, the mixing of the cells in the lymph node is more uniform, and increased numbers of more mature lymphocytes are especially prominent. These observations suggest that lymphocytes are being matured by the process indicated in chart 1. It is also pointed out that during the course of these events the predominating cell in the peripheral blood is the young, but not pathological, lymphocyte, corresponding to cells of the level of chart 1 labeled "large lymphocytes." It is felt that these facts constitute strong supporting data for the theory of Flemming and indicate the essential truth of the course of events in normal physiologic lymphopoiesis shown in chart 1. The importance of these observations will become more apparent in the subsequent consideration of lymphopoiesis in the non-infectious hyperplastic lymphatic states.

The normal physiologic stimulus for lymphopoiesis has not as yet been determined. Experimental procedures, such as light,^{17, 18} heat,¹⁹ roentgen-ray,^{20, 21} fat diets,²² extirpation of the spleen^{23, 24} and parenteral absorption of foreign proteins,²⁵ have all been shown to influence the peripheral level of lymphocytes, but none of these have been shown to be important in the physiologic or pathologic production of lymphocytic hyperplasias.

Equally obscure is the important selective mechanism by which certain lymphocytes are retained in the mother tissues and others are released to the lymph stream. It is clear that any intelligent attack upon the problem of the mechanism of production of the lymphatic dyscrasias is hampered by our lack of knowledge of these two fundamental physiologic processes.

THE PATHOLOGY OF LYMPHOPOIESIS IN NON-INFECTIOUS STATES

Although earlier investigators, particularly Haller,²⁶ had described whole blood which had the gross appearance of pus, it remained for Virchow²⁷ and

PLATE 1

Photomicrographs of paraffin sections of lymph nodes obtained by biopsy from cases of infectious mononucleosis and stained with hematoxylin and eosin.

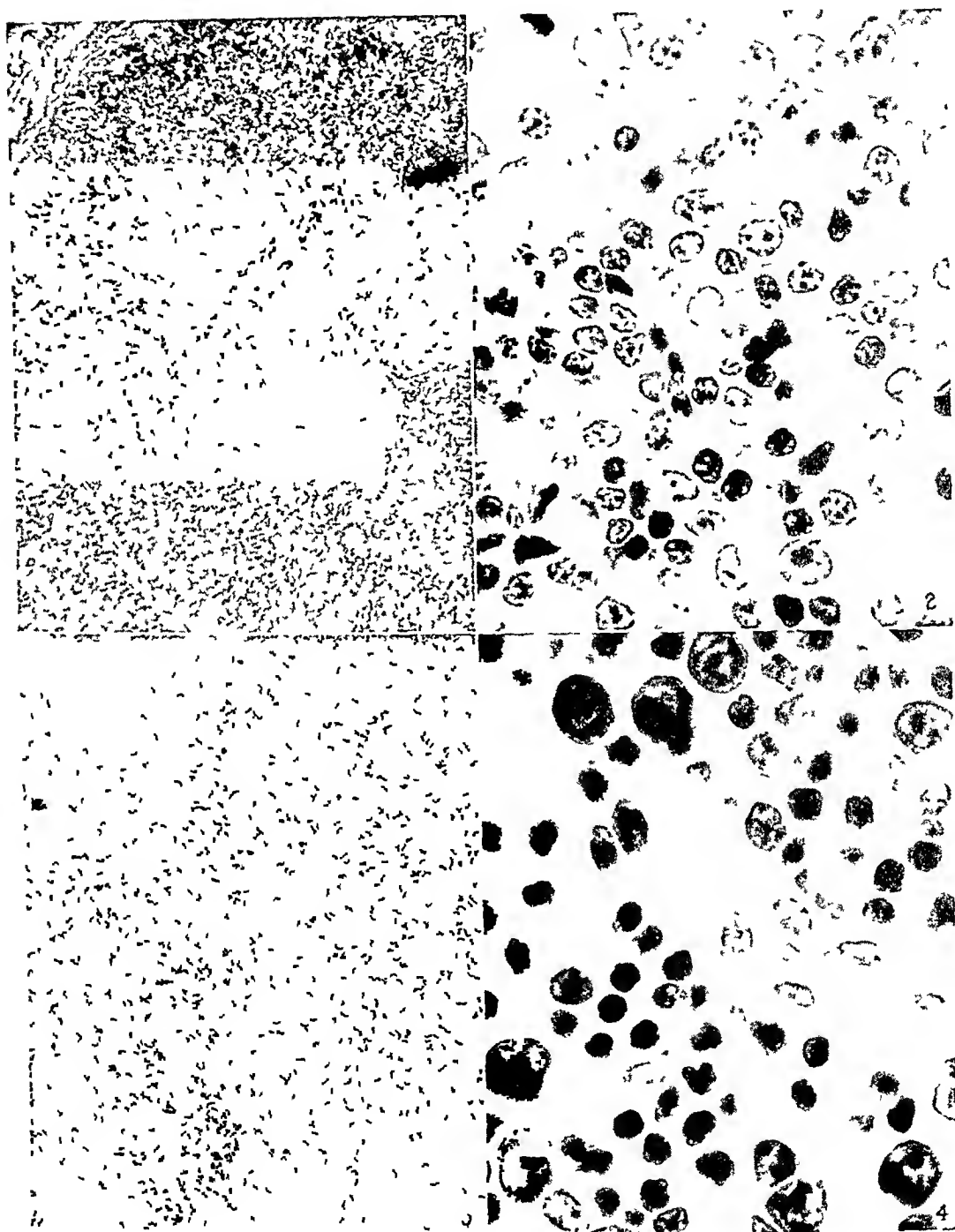
FIG 1 *Case C W Z* Low power view of a section through the cortex of the node. The capsule is seen in the upper left hand corner. Note the pale staining germinal center tissue which has invaded the entire node and is in direct continuity with the ill-defined secondary (germinal center) nodule seen in the upper center of the photomicrograph. This tissue was removed *early* in the course of the disease.

FIG 2 *Case C W Z* Oil immersion view taken through the edge of the secondary nodule referred to in the description of figure 1. The invasion of the peripheral zone of small lymphocytes (center of photograph) by germinal center tissue (upper part of photograph) is clearly shown. Mature lymphoid elements are in the minority.

FIG 3 *Case H W* Low power view of a section through the cortex of the node. This tissue was removed *late* in the course of the disease. The germinal center tissue is less prominent and is evenly mixed with the more mature cells of the node. Mature units now greatly outnumber the primitive cells and secondary follicles can no longer be delimited.

FIG 4 *Case H W* Oil immersion view taken from the same section as figure 3. The view is representative of all portions of the section. Note the predominance of matured cells as compared with figure 2, above, and the corresponding decrease in primitive-cell units. Large lymphoblasts with heavily basophilic cytoplasm and large prominent nucleoli are now particularly abundant. A vessel runs through the center of the section.

PLATE 1



Bennet⁻⁸ first to interpret correctly this phenomenon as characteristic of leukemia. John Bennet in 1845 described a case with autopsy report in which death took place from "the presence of purulent matter in the blood." Bennet recognized the non-inflammatory character of the mechanism by which it was produced, but he believed that the white corpuscles arose in a "blastema formed of liquor sanguinis" and did not divorce his theory entirely from that of suppuration. Virchow, however, immediately recognized his discovery as a new disease, "White Blood," emphasized its unique nature and cautiously suggested as the possible mechanism a diseased spleen which transformed red blood cells into white ones. In a later communication,²⁹ Virchow classified the diseases characterized by lymphatic hypertrophy into four groups: 1, leukemic lymphoma (lymphatic leukemia), 2, simple hyperplastic lymphoma (probably a mixture of pseudoleukemia and leukosarcoma), 3, lymphosarcoma, soft form (lymphosarcoma), and 4, lymphosarcoma, hard form (Hodgkin's disease). Virchow therefore laid the foundations for a clinico-pathologic classification of the idiopathic lymphatic hyperplasias which, with minor changes and amplifications, has held to the present day. Cohnheim,³⁰ using the term pseudoleukemia, separated from Virchow's soft form of lymphosarcoma a lymphatic state in which the gross and microscopic tissue changes of lymphatic leukemia were present but without the blood changes. Kundrat³¹ further clarified this group by his observation of cases in which the disease, originating in an isolated single lymphatic node, became locally invasive and later metastasized by way of the regional lymphatics. Finally Steinberg³² in a monumental contribution, the importance and significance of which has not been generally recognized, differentiated a group of cases of lymphosarcoma which started locally as an invasive tumor mass but which eventually became leukemic in that the abnormal cells composing the growth gained entrance to the blood stream causing a leukemia of the large cell type. Virchow's fourth group (Hodgkin's disease) is now generally regarded as primarily an infectious granuloma.³³ The observations of Steinberg,³⁴ the recent studies by L'Esperance in Ewing's laboratory,³⁵ as well as observations and experiments from our own laboratory tend to implicate the tubercle bacillus rather than other bacteria³⁶ or viruses^{37,38} as the initial causative agent.

This view of Hodgkin's disease is not, of course, necessarily in conflict with the fact that certain cases exhibit definite neoplastic characteristics. The phenomena of neoplasia arising in chronic lesions is not unusual in other tissues of the body. When neoplastic transformations occur in lymphoid tissues, however, the cell primarily involved is definitely not the lymphocyte, as suppression of lymphopoiesis with lymphopenia is an outstanding feature of the disease. Unpublished studies in our laboratory make it probable that either the reticulum cell, the monocyte or both are the elements in lymphatic tissue that undergo the characteristic pathologic changes. Hodgkin's disease, therefore, while a disease of lymphatic tissues, does not appear primarily to affect the lymphocyte itself and hence is not discussed further in this paper.

It is clear, therefore, that, with the exception of the separation of Hodgkin's disease from the group of primary lymphatic hyperplasias, little advance has been made toward an understanding of this group of diseases

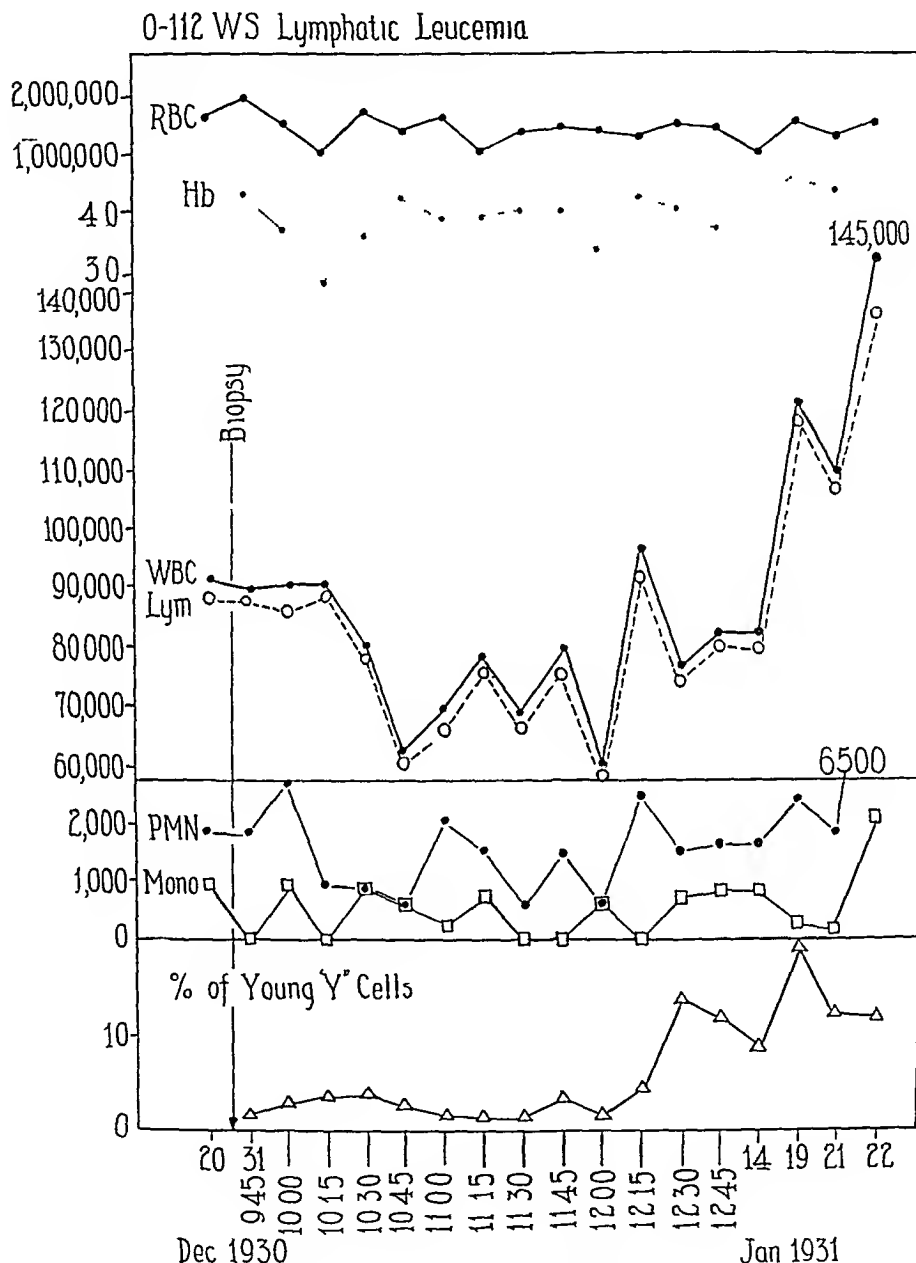


CHART 3 This graph shows the result of the blood findings in case W S who had lymphatic leukemia. Serial 15 minute counts during the period indicated do not show parallel fluctuations in "young" cells (as classified by maturative criteria shown to be valid for normal lymphopoiesis) and total numbers. From Jan 14 to 22 there was a rise in these "young" types but not in proportion to the rise in the totals. It is believed that these facts suggest that increase in proliferation of lymphocytes in this disease is marked by the production of cells which do not exhibit the maturative characteristics seen in cells produced by physiologic lymphopoiesis. Tissue from this case shown on plate 2, figure 1.

since Steinberg's significant contribution in 1908. We have today then four clinico-pathologic states which are characterized by lawless proliferation of the lymphatic type of cell viz, lymphatic leukemia, lymphatic pseudo-leukemia, leukosarcoma, and lymphosarcoma. By a critical analysis of typical cases from each of these classes we shall trace certain facts which apparently help to explain the mechanism responsible for lymphatic leukemia and which, at the same time, suggest a relationship of each of these lymphatic dyscrasias to the others. Cases in addition to those cited have been studied with entirely similar findings and conclusions. To conserve space, only data relevant to this discussion will be given.

CHRONIC LYMPHATIC LEUKEMIA

Case IV S This patient, a white male, aged 52 years, first came under our observation on Dec 20, 1930. He gave a history of general glandular enlargement, increasing pallor, and dyspnea of three years' duration. No history of a primary local lymph node enlargement could be obtained. Physical examination showed, in addition to the generalized adenopathy, an enlarged spleen, the border of which reached the level of the umbilicus. The enlarged nodes were elastic to the touch, freely movable, discrete and not painful on pressure. The blood examination showed the presence of pathologic lymphocytes in increased numbers, as shown in chart 3. These lymphocytes were all of the small round type, uniform in size, and each possessed a very narrow rim of cytoplasm containing small spherical (not rod-like) mitochondria about a nucleus that exhibited a characteristically heavy chromatin cloud and occasionally a small nucleolus. Studies of the delivery of the young lymphocytes, classified according to standards of proved value in appraising normal lymphopoiesis, failed to show during the serial 15 minute interval studies of Dec 31 any correlation between germinal center activity and intensity of lymphopoiesis (chart 3), in sharp contrast to the findings in infectious mononucleosis (chart 2). It is also clear from chart 3 that although the lymphocytes ranged between 60,000 and 90,000 on Dec 31 (from 9 45 a m to 12 00 noon), at no time during this interval did "young" cells constitute more than 3 per cent of the total.

PLATE 2

Photomicrographs of paraffin sections of lymph nodes removed at biopsy and stained with hematoxylin-eosin, oil immersion views. Figure 1 (chronic lymphatic leukemia) is to be contrasted with figure 2 (pseudoleukemia). Figure 3 (leukosarcoma) is to be contrasted with figure 4 (lymphosarcoma). The cells of figures 1 and 2 are morphologically identical, similarly identical are those of figures 3 and 4. Note, however, the vast differences between the cells of figures 1 and 2 and those of figures 3 and 4.

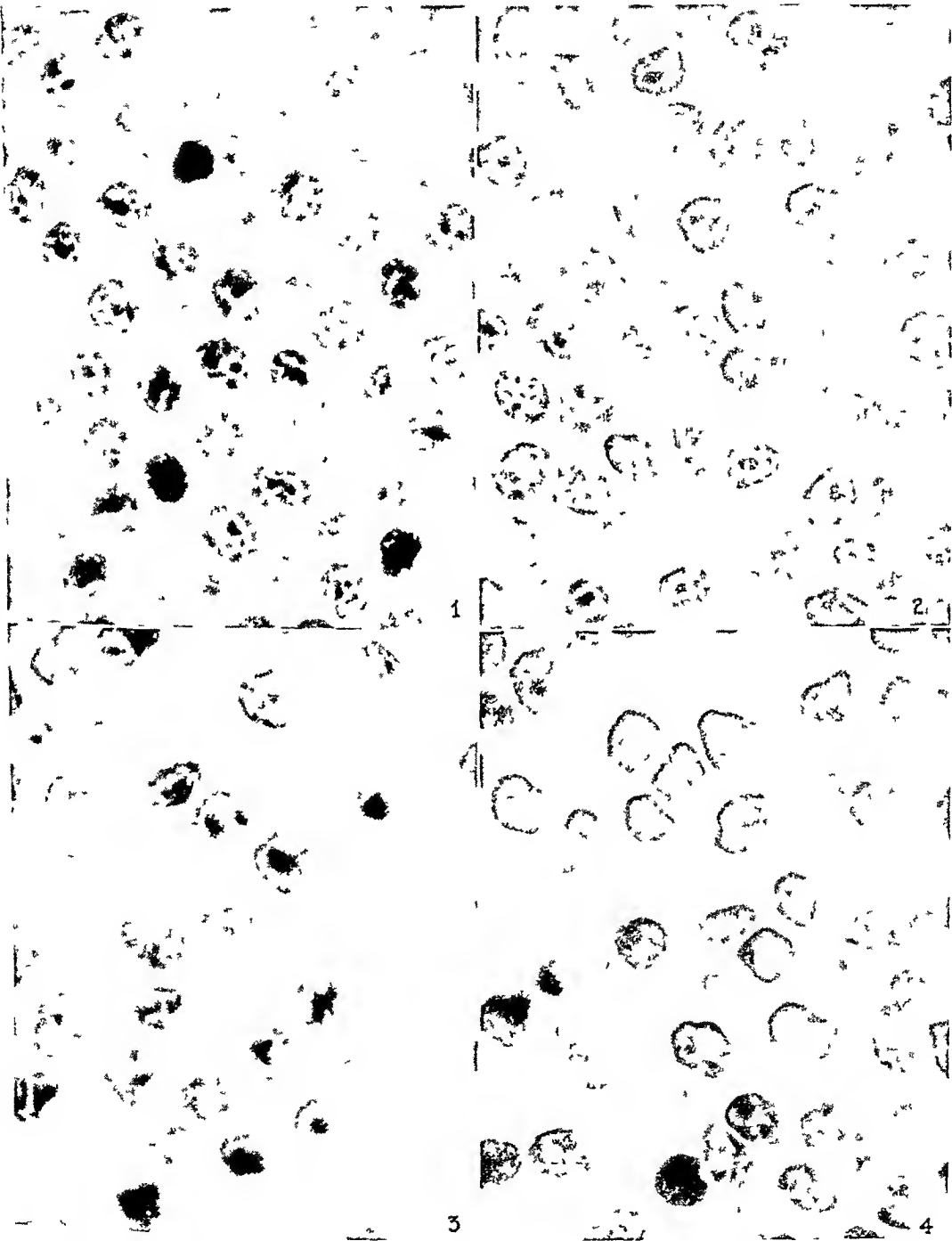
FIG 1 *Case IV S Chronic lymphatic leukemia* Note the endless reduplication of one type of cell with heavily chromatic nucleus and small but prominent nucleolus. The cells tend to be uniform in size and shape. No mitotic figures were found in this section, and there was no tendency to invade the capsule.

FIG 2 *Case R D B Lymphatic pseudoleukemia* The morphologic characters of the cells in this section were identical with those of figure 1.

FIG 3 *Case E M Leukosarcoma* These cells vary greatly in size and shape, tend to be vesicular and do not have the characteristic chromatin structure of those shown in figures 1 and 2. Mitotic figures were plentiful in this section. This tissue showed definite invasive characteristics and invaded the surrounding structures by direct extension. (See figure 1.)

FIG 4 *Case F M Lymphosarcoma* These cells correspond in all particulars with those shown in figure 3. Mitotic figures were particularly rich in the section from this patient, and the tissue was locally invasive.

PLATE 2



The obvious conclusion is that the lymphopoiesis of chronic lymphatic leukemia is not of the normal germinal center type. This fact, in conjunction with the observations that the cytoplasm of the immature cells is often relatively deficient in basophilic substance, and that the cells tend to divide by amitosis (mitotic figures are a great rarity in the blood and in sections of tissue from chronic lymphatic leukemia), suggests that multiplication of cells in this disease is chiefly by amitotic division with *minimal maturation*. In Chart 1 this would be indicated by proliferation of cells in a horizontal direction with very little progressive development vertically, that is to say, very little multiplication *with* maturation. It is clear that this hypothesis would account for small cell (chronic) leukemias as well as for the more acute large cell types, the difference being dependent upon the cell level at which the abnormal proliferation took place. It will be recalled that, physiologically, lymphocytes multiply at the various levels with some maturation arrest, but normally the reserve of cells at each stage remains small at any one time, the majority maturing promptly. In chronic lymphatic leukemia it would seem that this normal physiologic equilibrium is reversed so that division *with* maturation is quite small and division without maturation is correspondingly large. The end result is an overproduction of immature cells of no functional value to the body. In this respect the mechanism is similar to that observed in the over-production of megaloblastic tissue in pernicious anemia. An alternative theory in explanation of the horizontal proliferation of lymphocytes at immature levels in lymphatic leukemia is one which would link the mechanism with a neoplastic alteration. This hypothesis will be considered in the discussion of leukosarcoma.

LYMPHATIC PSEUDOLEUKEMIA (COHNHEIM)

Case R D B This patient, a white male aged 64, first came under observation on Dec 13, 1933, complaining only of generalized lymph gland swelling. Physical examination added only the fact that the spleen was enlarged to the costal border. The lymph nodes varied in size from a pea to a walnut and had exactly the same characteristics as described for patient W S above. Biopsy was performed with removal of a left cervical node on Dec 20, 1933. Both supravital examination and the study of fixed paraffin sections revealed hyperplasia with metaplasia of the lymphatic elements, indistinguishable from the tissue changes seen in classical chronic lymphatic leukemia and identical with the tissue from patient W S (Compare on plate 2 photomicrographs 1 from the tissue of W S and 2 from the tissues of R D B). The hematologic examination showed *absolutely no abnormalities* either in the quantitative values or in the qualitative characteristics of any of the circulating cell types. All lymphocytes were of the normal types, although repeated studies with both the supravital and fixed technics were utilized in an effort to detect pathologic variations. Chart 4 is a graph of the cellular equilibrium prevailing in this patient and shows that for the 25 months he has been under our observation no leukemic tendency has been observed. Roentgen-ray therapy in suitable dosage has been applied to the superficial glandular swellings as indicated on the chart in order to control the local enlargements. Throughout, this patient has been in the best of health and has continued to fulfill his occupation as a railroad crossing watchman.

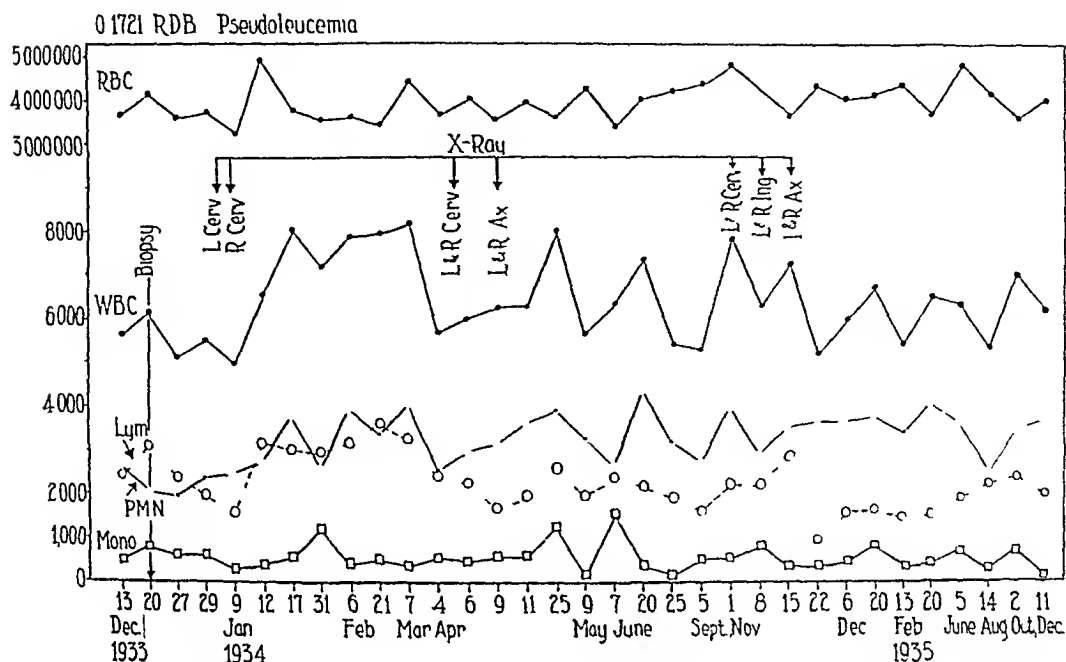


CHART 4 Results obtained by blood examination of patient R D B who had lymphatic pseudoleukemia. No abnormalities, either qualitative or quantitative, have been observed during the period of two years shown on this chart. Examination of a lymph node removed at biopsy on Dec 20, 1933 showed a histology indistinguishable from that of patient W S (chart 3) who had lymphatic leukemia with marked lymphemia. Local roentgen-ray treatments were given, as indicated on the chart, for the sole purpose of reducing the local swellings of the lymph nodes. Tissue shown on plate 2, figure 2.

From the facts as herein outlined the type of lymphatic hyperplasia is undoubtedly identical with that found in chronic lymphatic leukemia. In this patient, R D B, however, the barriers that allow only normally matured cells to gain entrance to the lymphatics and thence to the blood stream are effective in screening out the leukemic unmaturing types, thus confining them to the lymphatic tissues, whereas in the former case (W S) this mechanism has failed. The absence of leukemic cells in the peripheral blood in case R D B has resulted in an absence of infiltrative phenomena (large liver, anemia, etc.), as normal lymphocytes merely divide, mature and die and are not capable of endlessly dividing without maturing. Hence, unlike leukemic cells, normal lymphocytes do not crowd out, "infiltrate" and replace other tissue cells. It is clear that patient R D B is in good health and will continue so, as long as the leukemic cells do not gain entrance to the blood stream. That this screening mechanism may become ineffective at any time, thus converting the disease into a true leukemia has been observed by others^{39, 40}

LEUKOSARCOMA (STERNBERG)

Case E M This patient, a white child, aged 20 months, came under our observation Febr 11, 1935, eight weeks after the first evidence of the beginning of her illness. Pallor, dyspnea and generalized glandular enlargement with splenomegaly

developed rapidly. A careful history revealed that the first enlargement which appeared was a lump in the left submaxillary region. After a period of about four weeks there was an increase in the size of the spleen with a simultaneous enlargement of the lymphatic structures. A blood count six weeks before admission was said to have shown 35,000 white blood cells with the majority "mononuclear" leukocytes. Deep roentgen-ray therapy was applied over the mediastinum to relieve the dyspnea and reduce the number of cells. A careful hematologic examination made upon our first contact with the case revealed the classical findings of lymphatic leukemia with the one exception, that upon supravital examination it was possible to discriminate, after careful study, between two morphologically distinct types of lymphocytes existing side by side in the blood films. The one type was found not to depart from the normal in any recognized morphologic particular. The second type of lymphocyte

TABLE I

Important Supravital Criteria of Three Biologic Classes of Lymphocytes

CLASS	Characteristics of nucleus				
	Visible nucleoli	Chromatin distribution	Shape	Relative size of nucleus to cell	Nuclear membrane
Normal mature cell	Not prominent	Heavy cob web	Varies	Varies	Sharp
Leukemic cell	Prominent	Heavy splotches	Often bizarre	Tends to be large	Sharp
Sarcoma cell	Large	Fine cob-web	Round	Large	Indistinct

CLASS	Characteristics of cytoplasm			
	Quality	Neutral red vacuoles	Refractive vacuoles	Mitochondria
Normal mature cell	Faint yellow	Rose-red if present	None	Large rods or spheres
Leukemic cell	Limpid clear	Largely absent	None	Small spheres
Sarcoma cell	Faintly grey	1-10 highly refractive vacuoles about periphery of nucleus Deep scarlet when stained		Dust-like

CLASS	Other characteristics of cell			
	Motility	Approximate size	Phagocytosis	Fragility
Normal mature cell	Present	95% less than 9 microns	Absent	Slight
Leukemic cell	Absent	Varies	Absent	Marked
Sarcoma cell	Absent	12-14 microns	Absent	Moderate

present was definitely abnormal but differed from the normal in details other than those previously described as characteristic of the cells in chronic lymphatic leukemia. These pathologic cells ranged in size from 8μ to 15μ the majority being similar in size to the normal intermediate lymphocyte. The cytoplasm consisted of a narrow rim about the nucleus with a moderate sprinkling of dust-like mitochondria and contained from one to a dozen vacuoles which either did not stain at all or else took the vital neutral red with a reaction strongly to the acid side of its indicator range. The nucleus of this atypical cell was vesicular and contained a fine web-like chromatin



FIG 1 *Case E M Leukosarcoma* Low power view through submaxillary salivary gland adjacent to submaxillary lymph node. A portion of the lymph node lies in the upper right hand corner. The capsule of the node has been destroyed, and the lymphocytic elements have invaded by direct extension the submaxillary gland in the center and lower part of the section.

with a rather large nucleolus. The nuclear membrane was indistinct so that not infrequently there was some difficulty in sharply delimiting the area occupied by the nucleus. This cell we have called the "sarcoma cell" to distinguish it from the other types of lymphocytes described. Morphologically, in supravital preparations it is similar to proved sarcoma cells found in round cell sarcomata of the connective tissues. Table 1 by description compares this with the other lymphocytes mentioned in this paper.

The lymph node, removed at biopsy from the submaxillary region, differed

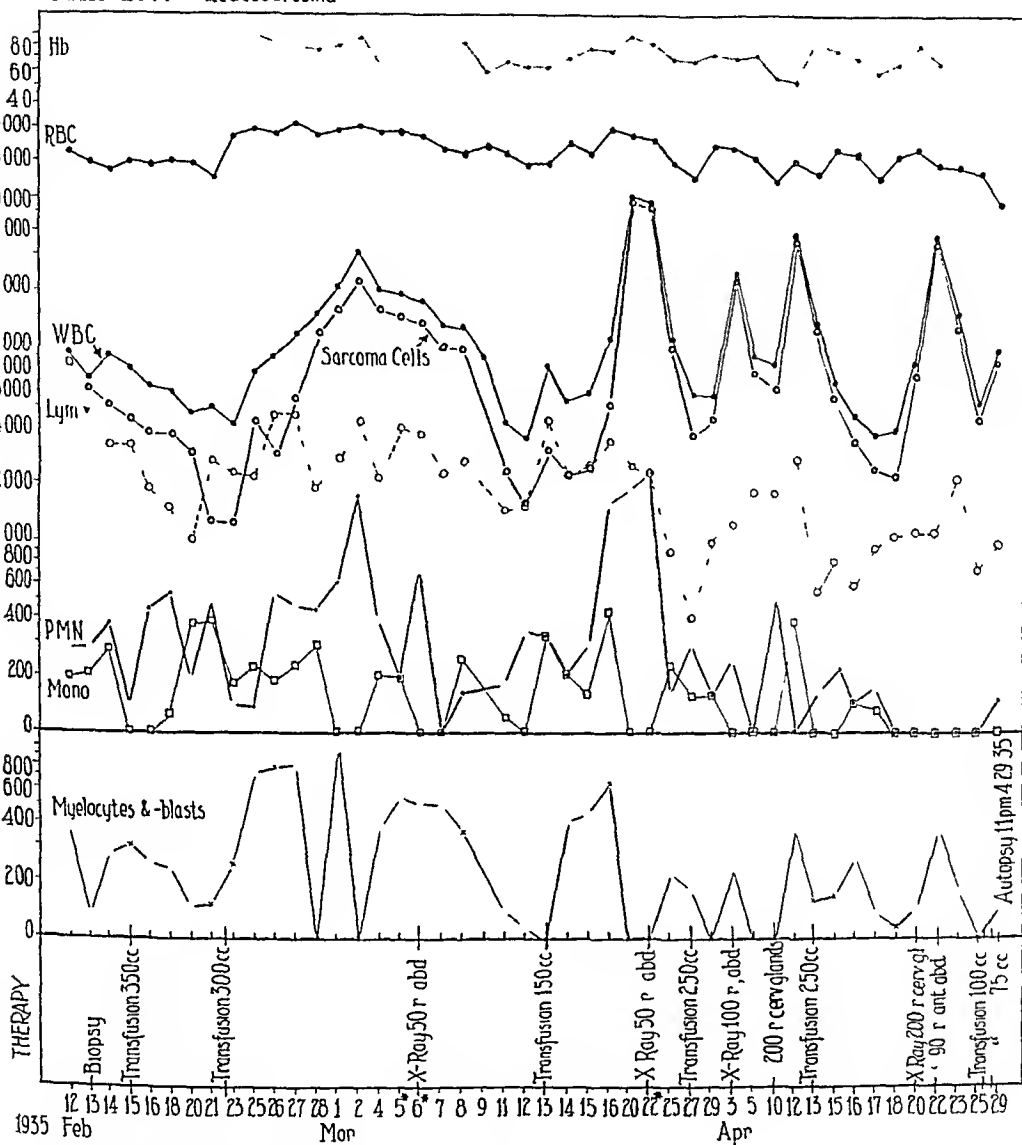
markedly from those found in the usual case of lymphatic leukemia. The lymph node could not be removed with capsule intact, as it was bound to the surrounding tissue. Upon cut section, the contents of the node were gray in color, extremely soft in consistency and very cellular. Supravital examination of scraping of this material showed a mixture of normal lymphocytes and cells corresponding to those found in the peripheral blood and designated as "sarcoma cells." Mitotic figures among the latter were very frequent. Paraffin sections showed characteristic sarcoma tissue. Remnants of secondary nodules were invaded and destroyed by these abnormal cellular elements. The proliferative process had broken through the capsule and invaded, in typically neoplastic fashion by direct extension, the adjacent parenchyma of the submaxillary gland. Figure 1 shows the characteristic invasiveness of these cells.

Chart 5 depicts graphically the course of the hematologic events as they occurred in this patient. In this chart the sarcoma cells are shown by the circles connected with a solid line, and the normal lymphocytes are shown by the circles connected with a dotted line. Several points on this chart are of interest and of importance to the theory of the mechanism of production of leukemia and will be discussed to the exclusion of other interesting data shown but not vital to the tenets of this paper.

It is clear that the excess of white cells consists entirely of the "sarcoma cell type" of lymphocyte, the curve representing the total leukocytes paralleling that representing the sarcoma cells. The curve for the normal lymphocytes constitutes a virtual plateau fluctuating for the most part between 2,000 and 4,000 cells and deviating downward from this level only once, when the sarcoma cells were at a very high level (60,000). This fall in the number of normal lymphocytes was probably due to a suppression of multiplication in the tissues (infiltrative phenomena) and not to a roentgen-ray effect, as it will be observed that a considerable drop in the red blood cells occurred at the same time, and that larger doses of roentgen-ray were given both before and subsequent to this fall without disturbing the level of either normal lymphocytes or red cells. It is also clear from this chart that the two kinds of lymphocytes shown have a quite marked difference in susceptibility to the destructive effects of the roentgen-ray (note in particular the behavior of these two cells to the treatment given on March 6). This further substantiates the biologic difference between them suggested by their morphologic characteristics. It is also evident that the extraordinary radiosensitivity of these sarcoma cells, transcending considerably even that of the normal lymphocytes, tends to place these cells in the category of neoplastic cells of lymphoid origin.

From the foregoing it would appear probable that the leukemia observed in patient E. M. is a type of lymphatic leukemia which differs from those already mentioned in at least three important respects: 1, in the morphologic characteristics of the abnormal lymphatic elements, 2, in their relative radiosensitivity, and 3, in the histo-pathology of the affected lymphatic tissues. These points all indicate a mechanism responsible for the leukemia of leukosarcoma which is different from that of simple lymphatic leukemia. This mechanism, as clearly indicated by the facts recited, points strongly to a neoplastic alteration of lymphopoiesis. This malignant lymphocyte then invades the blood stream (causing "leukemia") and infiltrates the various tissues of the body, giving rise to a clinical and

0 2420 EJM Leucosarcoma



* Micrometabolism of blood cells performed on these dates

CHART 5 Blood findings in patient E J M who had leucosarcoma. Particular attention is directed to the charting of two types of lymphocytes, one labeled "sarcoma cells" and the other "lymphocytes." The charting is upon semi-logarithmic scale. The normal lymphocytes at no time greatly exceed the value regarded as normal for the average person in health. The "sarcoma cells," however, between the periods in which roentgen-ray therapy was applied rise to high values, independently of the normal lymphocytes. The effectiveness of small doses of roentgen-ray in reducing the number of sarcoma cells and the relatively ineffectual results of these doses upon the normal lymphocytes are clearly shown and bespeak further for a biologic difference between these two types of lymphocytic cells. Tissues shown as figure 1 and also on plate 2, figure 3.

pathological picture simulating ordinary lymphatic leukemia. This mechanism exemplifies the third type of lymphocytosis which is theoretically possible according to the chart presented in the discussion of physiologic lymphopoiesis.

LYMPHIOSARCOMA (KUNDRA†)

Case F M This patient was a white male, aged 60, who was found to have "lumps" in his abdomen five months prior to the present observations. Physical examination on Febr 2, 1931 showed generalized swelling of the lymph nodes, including the mesenteric nodes. The nodes were discrete, rather hard, freely movable in some cases and fixed in others, but all were without tenderness to pressure. The spleen was enlarged to 5 cm below the costal border, and there was fluid in the abdomen. Gastrointestinal roentgen-ray series as well as other studies were negative. Repeated examinations of the blood showed no evidence of leukemic changes, either from a quantitative or qualitative standpoint (chart 6 shows two counts taken

F M Lymphosarcoma

	2-4-31	2-26-31	8-3-31
R B C	3,900,000	3,530,000	3,260,000
W B C	7,600	4,200	5,800
P M N	4,864	2,604	3,132
Lym	1,292	966	1,392
Mono	1,368	588	1,160

CHART 6 Three blood counts taken on patient F M who had lymphosarcoma. These were typical of the many observations that were made. No evidence of leukemic change is noted. Tissue shown on plate 2 figure 4.

early in the course of his disease and one near the end, typical of many that were made). Biopsy examination was made on Febr 3, 1931, and a lymph node 1 by 1 by 1½ cm removed from the left cervical area. The contents were very cellular, and from the characteristics of the cells examined supravivally a diagnosis of lymphosarcoma was made. Examination of the paraffin sections showed a type of cell histologically indistinguishable from that of the preceding case, E M (see plate 2, compare figures 3 (Case E M) and 4 (F M)).

A review of the pertinent facts in this case, typical of many such that have been observed, shows a lymph gland tumor originating in one part of the body (in this instance in the mesenteric area), which first spread locally and eventually became generalized, probably by metastasis. Clinically and histologically this case was identical with the preceding case (E M) except that the malignant cells were not continuously delivered into the circulation, with the result that neither a leukemic blood picture nor the infiltrative phenomena of leukemia developed. That some cases, starting in this manner, at times become leukemic^{12, 43} cannot be doubted. In such instances at some time, often following roentgen-ray therapy, the pathological cells undoubtedly gain free access to the blood—that is to say, leukosarcoma develops from the localized neoplastic alteration of the lymphoid cells characteristic of lymphosarcoma.

ALEUKOCYTHEMIC (ALEUKEMIC) LYMPHATIC LEUKEMIA

From the previous discussion, it may be inferred that there are three forces which determine the number of cells in the peripheral blood. In physiologic lymphopoiesis the level is determined by the balance which

exists between the factors of production, delivery to the blood stream and peripheral loss or destruction. For example, in infectious mononucleosis cases with marked adenopathy but with low total blood counts apparently reflect the existence of a very effective barricade which prevents release of these elements to the lymph and blood streams. This is not the result of high peripheral loss because examination of the cells in the blood stream reveals large numbers of relatively old lymphocytes, a fact which suggests accumulation rather than accelerated peripheral loss.

Careful study of the material accumulated in this laboratory has indicated that, in the diseases characterized by pathologic lymphopoiesis, the factor of peripheral loss of cells is manifested chiefly by tissue infiltration with blood cells, a circumstance which rarely, if ever, occurs to an important degree in the infectious lymphadenopathies.

The withdrawal of enormous numbers of cells from the blood and their storage in the tissue spaces have been outstanding features in some cases in which the blood has shown an actual leukopenia. In fact, in our experience a falling peripheral level of cells in chronic lymphatic leukemia has often been associated with the appearance of signs of heavy tissue infiltration, as shown by roentgen-ray examination of lung fields, an enlarging liver, a developing anemia and thrombopenia, etc. The clinical course, the roentgen-ray studies and the laboratory data in case J. B. illustrate this phenomenon clearly.

Case J. B. This patient with a peripheral level of cells which averaged 24,000 lymphocytes per cu. mm. of blood for two months just prior to June 15, 1935 had shown no evidences of infiltration (figure 2). The patient then had a spontaneous exacerbation of his disease with total counts rising to an average of 48,000 lymphocytes, with no further changes in the chest roentgen-ray as compared with previous examination. One month after this increase in the cell count occurred roentgen-ray therapy was given until the peripheral count became stabilized at an average level of 21,000 lymphocytes. This level persisted for 12 days. During the nine days after the establishment of this plateau of 21,000 the count slowly fell spontaneously to an average level of 8,000 lymphocytes. Dyspnea and cyanosis slowly became more evident during the next 17 days, and one month after the spontaneous development of the aleukemic phase, respiratory distress was marked. A roentgen-ray at this time, with a lymphocyte count of 6,083 on Nov. 14, 1935, showed marked infiltration in the right lower lung field (Figure 3). This was treated with deep roentgen-ray locally with some clearing of the cellular infiltration, but without much clinical relief. A roentgen-ray taken 15 days later, Nov. 29, 1935, showed spread of the infiltrative process to the left lung (Figure 4). Throughout the aleukemic phase, which persisted 34 days until his death, the lymphocytes maintained an average level of 8,000 cells. There was no increase in size of the lymph nodes during this phase.

This discussion provides an explanation of the mechanism resulting in the so-called aleukemic types of lymphatic leukemia. In some cases with large lymph nodes but low peripheral cell count the "screening" mechanism in the lymph nodes is probably particularly efficient. These cases resemble the pseudoleukemic types exemplified by case R. D. B. previously discussed, the difference being in the relative efficiency of this mechanism. Some

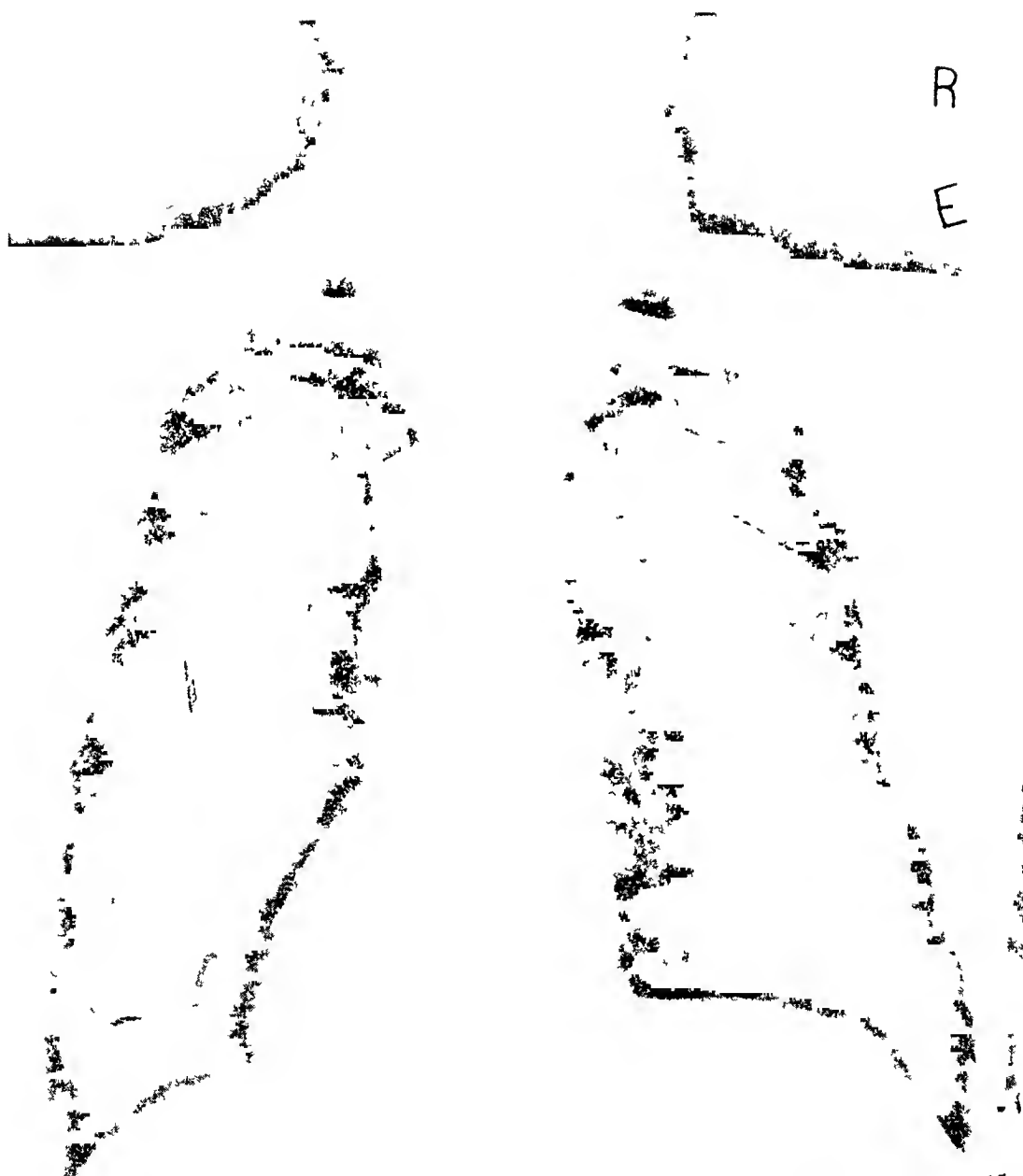


FIG 2 *Case of J B Ateleukemic lymphatic leukemia* Chest plate taken on June 15, 1935 The tracheo-bronchial lymph nodes about the right and left hilus are enlarged, but the lung fields are clear



FIG 3 Case of J B A leukemic lymphatic leukemia Chest plate taken on Nov 14 1935 Heavy infiltration of cells shown particularly in right lower lobe Beginning infiltration in left side



FIG 4 Case of J B Aleukemic lymphatic leukemia Chest plate taken on Nov 29, 1935 Deep roentgen-ray therapy given on Nov 16 resulted in some clearing of the involvement on the right side However, the left side is now heavily infiltrated, particularly at the base

cases, treated with roentgen-ray therapy with marked reduction in adenopathy, persist over long periods of time with low total counts and very little evidence of lymph node enlargement. Such cases are probably examples of aleukemic leukemia in which the proliferative forces have been reduced in activity. Other cases, with leukopenia developing after having shown previously high peripheral cell counts, may show marked evidences of infiltrative phenomena. These represent instances of aleukemic lymphatic leukemia in which loss of cells from the blood stream to the tissue spaces is particularly important. In this latter type it seems probable that the rate of production of the cells is not sufficiently high to balance the peripheral loss.

A consideration of these facts, therefore, suggests that, at times, in individual cases, any one of the three physiologic forces which are important in determining the peripheral level of cells may be the chief factor in the production of the so-called aleukemic state of lymphatic leukemia. The significance of analyzing each case from these standpoints for determining prognosis is obvious.

DISCUSSION

From the observations made in the above cases, each cited as type specific for its class, it would seem that there are at least three mechanisms by which lymphoid tissue becomes hyperplastic: first, by excessive multiplication and maturation occurring simultaneously (e.g., infectious mononucleosis), second, by excessive multiplication with little or no concurrent maturation (e.g., the common types of lymphatic leukemia and pseudo-leukemia), and third, by the metaplasia of cells with neoplastic alteration (e.g., lymphosarcoma). Each of these three basic pathologic states has been observed to occur in man. Cases of infectious mononucleosis with normal or nearly normal peripheral blood counts have been observed in our clinic (aleukocythemic infectious mononucleosis), whereas the lymphemia in other cases has been so marked as to make the differential diagnosis between lymphatic leukemia and infectious mononucleosis a matter largely dependent upon a careful qualitative study of the individual lymphatic cells. In these latter cases the determination of a continuance of normal maturation and the absence of amitotic division in the cells (inactive nuclei) have been among the important differential criteria. Important to this discussion is the fact that the phenomenon of cellular infiltration (marked anemia, thrombopenia, large liver, etc.) has never been observed in this disease because 1, the cells are more mature and have correspondingly lowered potentialities for division, and 2, the cells continue to mature and hence tend to fulfill their life cycle, dying in large numbers. These factors discourage local growth tendencies in the tissue spaces where the cells may lodge, so that the phenomenon of infiltration (which largely represents in the last analysis local growth) is not seen in infectious states. In direct contrast with physiological lymphopoiesis as illustrated by infectious

mononucleosis, pathological lymphopoiesis is remarkable in that observed maturation of these cells is minimal in amount, whereas the evidence indicating profound propensities for division is an outstanding feature

The evidence introduced in the body of this paper would seem to make it necessary, in order adequately to explain the phenomena observed, to hypothecate two distinct types of mechanisms responsible for the pathological lymphatic hyperplasias. On the one hand, cytologic and histologic evidence indicates that in one type of lymphatic hyperplasia, the mechanism is neoplastic (lymphosarcoma and leukosarcoma). On the other hand the evidence secured by parallel methods of examination in the other group

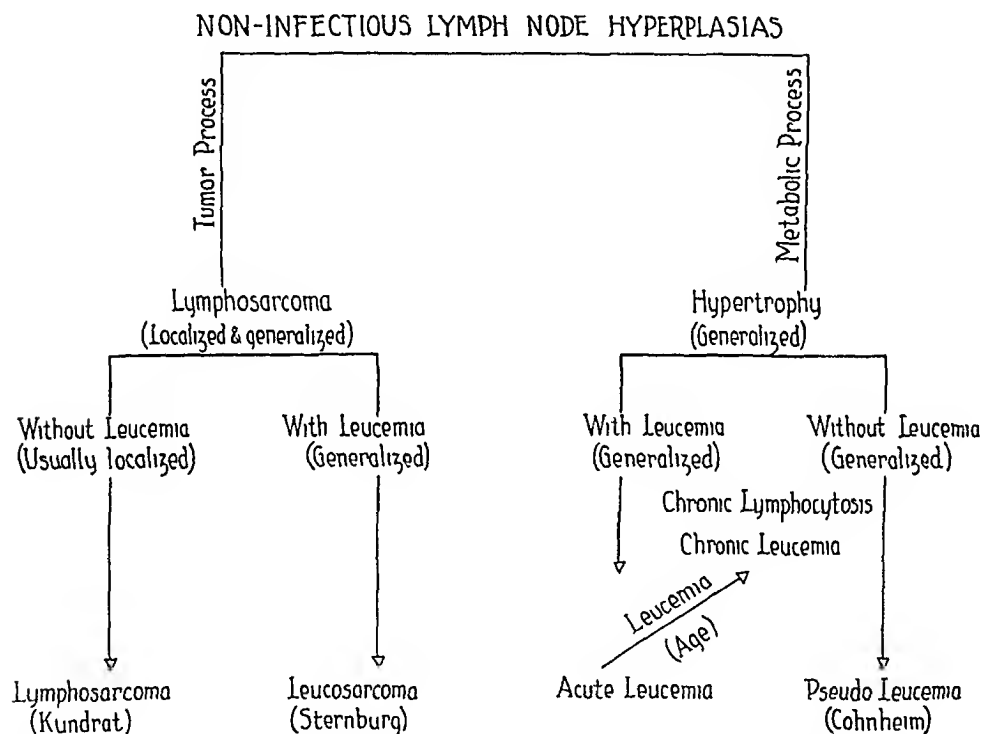


CHART 7 Graphic representation of the author's conception of the interrelationships existing between the primary non-infectious lymphocytic diseases. This scheme suggests that all of the lymphocytic hyperplasias of non-infectious origin consist essentially of two groups, that which is directly traceable to a neoplastic alteration in the reacting unit, the lymphocyte, and that group which is characterized by unlimited proliferation of lymphocytic elements resulting from an unknown but not a neoplastic mechanism. Either group may or may not exhibit leukemia.

(leukemia and pseudoleukemia) indicates that the mechanism is neither neoplastic in the same sense that lymphopoiesis is neoplastic in lymphosarcoma, nor essentially physiologic as in infectious states. In this latter (leukemic-pseudoleukemic) group the chief characteristic seems to be division without concomitant maturation, yet, withal, not neoplastic in character. The prototype of pernicious anemia immediately is recognized, and it is believed upon the basis of the evidence which we have secured that this type of lymphatic leukemia may be the result of a mechanism similar to

that which is responsible for the production of pernicious anemia. In order to account for the obviously neoplastic character of lymphosarcoma and leukosarcoma, it is necessary to postulate a second mechanism for the production of leukemia, that is, a neoplastic alteration in the lymphocytes which sometimes gain access to the blood stream (leukosarcoma). Lymphatic leukemia, according to this hypothesis which seems necessary to bring all the observed facts about this disease into accord, is the result of two vastly different etiologic agencies, the one neoplastic, the other possibly metabolic. The leukemias of the former type are usually more acute whereas those of the latter may be acute but usually are chronic. *The majority of the cases of chronic lymphatic leukemia are thus believed to be of metabolic origin.* Chart 7 illustrates the author's conceptions of the interrelationships of the various types of non-infectious lymphatic hyperplasias. Only those diseases which primarily affect the lymphocyte as such are shown.

It is emphasized that the conclusions as given above are not necessarily at variance with the well established data obtained from experimental leukemia in animals. The transmissibility of tumors in mice^{44,45} and chickens,⁴⁶ which in some instances show lymphatic leukemia and in others lymphosarcoma without leukemia, is simply a repetition of the same phenomena observed in man under the lymphosarcoma-leukosarcoma sequence described by Sternberg in 1908. In the case of chickens, many of the so-called leukemic states are undoubtedly the response to infectious agents⁴⁷ and are therefore not true leukemias but rather lymphocytoses. Similar states in man, difficult to differentiate from true leukemias, are regularly observed⁴⁸ (see also discussion concerning infectious mononucleosis). It is not believed, however, that any of the true leukemias of man are the result of infectious agents for the various reasons given in previous chapters concerning the mechanism of the production of the cells in leukemia and their physical characteristics.

CONCLUSIONS

1 All theoretically predictable variations in lymphopoiesis probably occur in man. Each type may give rise to nearly the same clinico-pathologic syndrome, but essential differences can be determined and established by a study of the physical characteristics of the cells involved.

2 A study of cases showing pathologic lymphopoiesis points to the concept that there are probably two etiologic forces responsible for lymphatic leukemia in man which operate through two different mechanisms, the one neoplastic, the other metabolic.

3 Analysis of the question of idiopathic lymphatic hyperplasias indicates that there are only two fundamental types: (a) neoplastic alterations of the lymphocyte without leukemia (lymphosarcoma) and with leukemia (leukosarcoma), and (b) "benign" hypertrophies without leukemia (lymphatic pseudoleukemia) and with leukemia (some of the acute cases and probably most of the chronic lymphatic leukemias).

4 Many acute leukemias are not true leukemic transformations of the underlying lymphatic tissues but are simply a vigorous cellular response to infectious agents conditioned by the host, the infectious agent, or both

5 Aleukocythemic (aleukemic) leukemia may be the result of either type of mechanism which can produce lymphatic leukemia, but in all cases a low peripheral level of the lymphatic elements in the blood, when the stimulus to lymphopoiesis is strong, is the result either of a partially effective mechanism which normally is completely effective in preventing pathologic and immature cell-forms from leaving the mother tissues and entering the blood stream, or rapid migration of the pathologic cells from the blood into the tissue spaces

BIBLIOGRAPHY

- 1 CUNNINGHAM, R S, SABIN, F R, and DOAN, C A The development of leukocytes lymphocytes, and monocytes from a specific stem-cell in adult tissues, Carnegie Inst of Washington, Publication No 361, Contrib to Embryol No 84, 1925, xvi, 227-276
- 2 WISEMAN, B K Criteria of the age of lymphocytes in the peripheral blood, Jr Exper Med, 1931, liv, 271-294
- 3 WISEMAN, B K The identity of the lymphocyte, Folia haemat, 1932, xli, 346-358
- 4 FLEMMING, W Studien über Regeneration der Gewebe, Arch f mikr Anat, 1885, xiv, S 5 and 355
- 5 MARCHAND, F Über die Herkunft der Lymphozyten und ihre Schicksale bei der Entzündung, Verhandl d deutsch path Gesellsch, 1913, xvi, 5
- 6 HELLMANN, T J Studien über das Lymphoide Gewebe, Ziegler's Beitr, 1921, lxxviii, 333
- 7 HEILMANN, P Über die Sekundärfollikel im Lymphatischen Gewebe, Virchow's Arch f path Anat, 1926, cclviii, 160
- 8 LATTI, J S The interpretation of the so-called germinal centers in the lymphatic tissue of the spleen, Anat Rec, 1922-23, xiv, 233
- 9 HEIBERG, K Über die Phagocytosecentra des Lymphoiden Gewebes und über die Lymphocytenproduktion, Acta med Scandinav, 1927, lxxv, 443
- 10 POL, S Zur Funktionsfrage der Lymphadenoiden Organe, insbesondere der Tonsillen, Verhandl d deutsch path Gesellsch, 1923, xix, 286
- 11 ASCHOFF, L Die lymphatischen Organe, Beiheft z Med Klin, 1926
- 12 GROLL, H, and KRAMP, F Involutionvorgänge an den Milz-follikeln, Zentralbl f Path, 1920-21, xxxi, 145
- 13 MAXIMOW, A Special cytology, edited by E V Cowdry, 2 Ed, 1932, Paul B Hoeber, Inc, New York, pp 603-711
- 14 BUNTING, C H, and HUSTON, J Fate of the lymphocyte, Jr Exper Med, 1921, xxxiii, 593
- 15 LEE, F C Changes in the number of small lymphocytes of the blood following ligation of the thoracic duct, Jr Exper Med, 1922, xxxvi, 247
- 16 KINDWALL, J A A supravital study of the cells in the lymph stream of the rabbit, Bull Johns Hopkins Hosp, 1927, xl, 39-51
- 17 WICKLINE, W A The effect of tropical sunlight on the white count, Mil Surgeon, 1908, xxiii, 382
- 18 CLARK, J The action of light on the leukocyte count, Am Jr Hyg, 1921, i, 39-62
- 19 MURPHY, J B, and STURM, E The effect of dry heat on the blood count in animals, Jr Exper Med, 1919, xxix, 1
- 20 THOMAS, M M, TAYLOR, H O, and WITHERBEY, W D X-ray effects, stimulative action on lymphocytes, Jr Exper Med, 1919, xxiv, 75

- 21 NAKAHARA, W, and MURPHY, J B Studies on x-ray effects, Jr Exper Med, 1922, *xxx*, 475
- 22 SETTLES, E L The effect of high fat diet on growth of lymphoid tissue, Anat Rec, 1921, *xx*, 61-83
- 23 MATHEW, E, and MILES, A Observations on the blood changes subsequent to excision of the spleen following traumatic rupture, Edinburgh Med Jr, 1907, *xii*, 294
- 24 PFARCE, R M, KRUMBHAAR, E B, and FRAZIER, C H The spleen and anemia, 1918 Lippincott, Philadelphia
- 25 WISEMAN, B K The induction of lymphocytosis and lymphatic hyperplasia by means of parenterally administered protein, Jr Exper Med, 1931, *liii*, 499-510
- 26 HALLER, P Elementary physiology, Tom 11, 14-16 (Quoted by Virchow)
- 27 VIRCHOW, R Weisses Blut, Neue Nat a d Geb d Nat u Heilk, Weimar, 1845, *xxv*, 151
- 28 BENNET, J H Case of hypertrophy of spleen and liver in which death took place from suppurative of the blood, Edinburgh Med and Surg Jr, 1845, *liiv*, 413-423
- 29 VIRCHOW, R Die krankhaften Geschwulste, 1864-65, A Hirschwald, Berlin, p 11
- 30 COHNHEIM, J Ein Fall von Pseudoleukämie, Virchow's Arch f path Anat, 1865, *xxviii*, 451
- 31 KUNDRAT, H Über Lympho-Sarkomatosis, Wien klin Wchnschr, 1893, *vi*, 211
- 32 STERNBERG, C Über Leukosarkomatose, Wien klin Wchnschr, 1908, *xxi*, 475-480
- 33 KRUMBHAAR, E B Is typical Hodgkin's disease infection or neoplasm? Am Jr Med Sci, 1934, *clxxxviii*, 597-604
- 34 STERNBERG, C Über eine Eigenartige unter dem Bilde der Pseudo-leukämie verlaufende Tuberculose des lymphatischen Apparates, Ztschr f Heilk, 1898, *xix*, 21
- 35 L'ESPERANCE, E Experimental inoculation of chickens with Hodgkin's nodes, Jr Immunol, 1929, *xvi*, 37-60, also 27-36, also 1933, *xviii*, 127 Ibid, 1930, *xviii*, 127, 133
- 36 BUNTING, C H, and YATES, J L Cultural results in Hodgkin's disease, Arch Int Med, 1913, *xii*, 236
- 37 GORDON, M H Rose research on lymphadenoma, 1933, William Wood and Co, Baltimore
- 38 VAN ROOYEN, C E Recent experimental work on the etiology of Hodgkin's disease, Brit Med Jr, 1933, *i*, 562, 644
- 39 FRAENKEL, E Über die sogenannte Pseudoleukämie, Verhandl d deutsch path Gesellsch, Jena, 1912, *xv*, 5-21
- 40 STERNBERG, C Ibid, 22-41 and 55-59
- 41 WARBURG, O The metabolism of tumors, 1930, Constable and Co, Ltd, London
- 42 WEBSTER, L T Lymphosarcoma, lymphatic leukemia, leukosarcoma, Hodgkin's disease, Johns Hopkins Hosp Rep, 1921, *xx*, 251-313
- 43 KATO, K, and BRUNSCHWIG, A Acute leukemia following lymphosarcoma, Arch Int Med, 1933, *li*, 77-89
- 44 FURTH, J, SEIBOLD, H R, and RATHBONE, R R Experimental studies on lymphomatosis of mice, Am Jr Cancer, 1933, *xiv*, 521-604
- 45 SLYE, M Relation of heredity to occurrence of spontaneous leukemia, pseudoleukemia, lymphosarcoma and allied disease in mice, Am Jr Cancer, 1931, *xv*, 1361-1386
- 46 ELLERMAN, V The leukosis of fowls and leukemia problems, 1921, Gyldendal, London
- 47 CASH, J R, and DOAN, C A Spontaneous and experimental infection of pigeons with *B acutycke*, Am Jr Path, 1931, *vii*, 373-397
- 48 KRUMBHAAR, E B Leukemoid blood pictures in various clinical conditions, Am Jr Med Sci, 1926, *clxxii*, 519-532

METABOLISM STUDIES IN MYASTHENIA GRAVIS BEFORE AND DURING THE ADMINISTRATION OF GLYCINE *

By MILDRED ADAMS, Ph D , MARSCHELLE H POWER, Ph D , and WALTER
M BOOTHBY, M D , F A C P , *Rochester, Minnesota*

SEVERAL attempts have been made to discover specific metabolic abnormalities in subjects with myasthenia gravis. The results in general have been contradictory and therefore inconclusive. The therapeutic value of glycine in this disease has caused a renewed interest in such studies, although the majority of the more recent investigations have dealt chiefly with the effect of glycine on the excretion of creatinine and creatine.

This investigation was undertaken, accordingly, to gain more complete information concerning the metabolism of patients with myasthenia gravis both before and during the administration of glycine. Complete studies in which the food, urine, and feces have been carefully collected and analyzed have been carried out on two subjects.

EXPERIMENTAL

Subject 1 was a woman, 40 years of age, who weighed 75.2 kg and whose height was 5 feet and 8 inches (173 cm). She had had myasthenia gravis for at least 10 years and for three years had been practically bedridden, until treatment with ephedrine was begun. Since that time she had been slowly improving, and at the time of this investigation she could get about fairly well with the aid of a wheel chair. She was still taking ephedrine—one 3/8 grain (0.025 gm) capsule of ephedrine sulphate twice daily—when she came to the clinic, and this medication was continued throughout the study. The patient was placed on a constant diet containing 12.2 gm nitrogen and about 1750 calories. The investigation consisted of a preliminary period of three days to allow the patient to come to equilibrium with the new diet, a control period of four days (I¹) † and a period of 11 days (II¹) on the diet plus 40 gm glycine (7.40 gm nitrogen) daily. At the end of this time the subject was unable to continue this regimen and the nitrogen of the diet was reduced to 10.7 gm and the glycine to 20 gm (3.70 gm nitrogen) daily. After an interval of two days, collections of urine and stool were again resumed for a third period of 10 days (III¹).

Subject 2 was a man 24 years of age, who weighed 66.9 kg, and whose height was 5 feet and 8½ inches (174 cm). Symptoms of myasthenia gravis first had been noted at the age of 15 years and had continued intermittently for about eight years. During the year before the patient's registration at the clinic, he had not been free of symptoms, and on admission he was extremely weak, had great difficulty in swallowing, and was confined to bed. For about one month he had been taking ephedrine sulphate, 3/8 to 3/4 grain (0.025 to 0.05 gm) thrice daily. This medication was reduced to 3/8 grain (0.025 gm) twice daily and was maintained at that level during our studies. This subject was placed on a constant diet containing 8.5 gm nitrogen and about 1900 calories. After a control period of four days (I²) there followed a period of 12 days (II²) on the diet, plus 30 gm glycine daily (5.56 gm nitrogen). At the end of this period it became necessary to institute tube feeding, and the metabolic studies were, therefore, discontinued.

* Submitted for publication December 9, 1936. From the Mayo Clinic, Rochester, Minn.

† The significance of these symbols is evident in the table.

The complete output of urine was collected for each 24 hours and the nitrogen and sulphur partition products were usually determined immediately, although in a few instances it was necessary to use aliquot portions of mixed, two-day specimens. Aliquot portions of four to six consecutive specimens were acidified and mixed for the determination of the inorganic constituents. An exact duplicate of the 24 hour diet was ground and thoroughly mixed, dried in a current of air at about 70° C, and again ground and mixed to obtain samples suitable for analysis. Two separate 24 hour samples of food were prepared in this way for each of the different diets used. All uneaten food was collected, dried in a manner similar to that described and analyzed so that accurate corrections of the intake were possible. The feces were collected for periods of from four to six days and an enema of warm, distilled water was used to close each period. Hydrochloric acid was added to prevent loss of nitrogen and the specimens were prepared for analysis by drying in a current of warm air at 70° C. The following methods of analysis were used: total nitrogen, macro-Kjeldahl, urea, manometric determination of carbon dioxide after treatment with urease (Van Slyke¹⁷), ammonia, aeration and titration (Van Slyke and Cullen¹⁸), preformed creatinine (Folin⁹), total creatinine, the method of boiling with picric acid (Folin⁶), uric acid (Folin^{8,9}), total amino acid (Van Slyke¹⁶ volumetric method, using an apparatus modified according to Koch¹¹). For the determination of total sulphur in urine 10 cc. was completely ashed with fuming nitric acid in an apparatus similar to that of Rossenbeck.¹³ The ashed solution was evaporated to dryness with the addition of water and hydrochloric acid to remove the excess nitric acid. The dry residue was then taken up in 5 or 10 cc. of 87 per cent trichloroacetic acid and the sulphate present precipitated as the benzidine salt, essentially as described by Hubbard.¹⁰ After centrifuging and washing, the benzidine sulphate was titrated with 0.01-normal sodium hydroxide. The inorganic fraction was similarly precipitated as benzidine sulphate from urine appropriately diluted with trichloroacetic acid. Hydrolysis of conjugated sulphates was accomplished by heating the trichloroacetic acid dilutions in calibrated tubes for 15 minutes in boiling water. The trichloroacetic acid lost by decomposition was replaced by the addition of a predetermined quantity of 40 per cent solution, the mixture made to a definite volume, and the sulphate present, inorganic plus conjugated, was precipitated and titrated as the benzidine salt. From these determinations the neutral sulphur and conjugated sulphate fractions were found by calculation. For the determination of total sulphur in food and feces suitable samples were burned in an oxygen bomb according to Berthelot as described by Sherman,¹⁴ after which the sulphate in the bomb washings was precipitated and weighed as barium sulphate.

The inorganic constituents of urine, food and feces were determined on hydrochloric acid extracts of samples which had been ashed in platinum in an electric muffle at 450° C. The colorimetric method of Fiske and Subbarow⁵ was used for the determination of phosphate. In the case of urine the inorganic phosphorus as determined in unashed samples agreed with the determinations on the ashed samples within 1 or 2 per cent. Calcium and potassium were determined according to Tisdall and Kramer.¹⁵ Magnesium was precipitated as magnesium ammonium phosphate according to Tisdall and Kramer, after which the phosphate in the precipitate was determined by Fiske and Subbarow's method. Butler and Tuthill's⁴ adaptation of the zinc uranium acetate method of Barber and Kolthoff³ was used for the determination of sodium.

RESULTS

The results of the balance studies are summarized in table 1 in terms of the average daily balances for the control periods and the periods during which glycine was administered. In period I¹ for subject 1 the balances

TABLE I
Balance Studies in Myasthenia Gravis

Constituent	Subject 1 *				Subject 2 †			
	Period I ¹ four days, no glycine		Period II ¹ eleven days, 40 gm glycine daily = 7.40 gm nitrogen		Period I ² four days, no glycine		Period II ² twelve days, 30 gm glycine daily = 5.56 gm nitrogen	
	Daily intake, gm	Daily balance, gm	Daily intake, gm	Daily balance, gm	Daily intake, gm	Daily balance, gm	Daily intake, gm	Daily balance, gm
Nitrogen	12.20	-0.02	19.60	-0.03	8.20	-3.91	13.52	-3.11
Sulphur	0.89	+0.04	0.89	+0.01	0.70	-0.16	0.69	-0.14
Phosphorus	1.25	+0.08	1.25	+0.05	1.13	-0.26	1.10	-0.21
Sodium	3.38	+1.33	3.38	+0.49	2.44	+0.20	2.45	+0.23
Potassium	2.52	-0.49	2.52	-0.19	2.98	+0.02	2.88	-0.08
Magnesium	0.20	-0.02	0.20	-0.01	0.19	-0.02	0.21	-0.01
Calcium	1.07	+0.15	1.07	+0.17	0.86	-0.19	0.83	-0.20

* Three-fourths grain (0.05 gm) ephedrine sulphate daily. Course of disease: condition stationary, slight but insignificant loss in weight.

† Three-fourths grain (0.05 gm) ephedrine sulphate daily. Course of disease: condition progressively getting worse with marked loss of weight—3 kg.

for nitrogen, sulphur, phosphorus, magnesium, and calcium were close to equilibrium. Likewise during period II,¹ when glycine was administered, there was remarkably little change in these balances. In a subsequent period, not shown in table 1, during which time the intake of food and glycine was reduced, the balances continued to be much like those observed for period II¹. Apparently there was a large retention of sodium in period I¹ but this may be ascribed to the fact that the supplementary sodium chloride of the diet was not sufficiently accurately weighed during this period. The retention of sodium in period II¹ was 0.49 gm per day, a value not abnormally high in view of the fact that no correction for loss of sodium through the skin could be made. The potassium balance in period I¹ appeared to be significantly negative. In period II¹ this balance became somewhat less negative.

In contrast to subject 1, subject 2 was, during the control period, in definite negative balance as regards nitrogen, sulphur, phosphorus, and calcium, but in approximate balance as regards potassium, magnesium, and possibly sodium. During the administration of glycine, period II,² the loss of nitrogen decreased but the balance was still highly negative. No marked changes occurred in the balances of the other constituents.

The data concerning the nitrogen partition products in the urine are summarized in table 2 in terms of the average daily values. For the purpose of showing in greater detail the changes in distribution during the periods of administration of glycine, the results of the daily determinations

TABLE II
Nitrogen Partition Products in the Urine before and during the Administration of Glycine

Period	Days	Glycine nitrogen, gm	Food nitrogen, gm	Total nitrogen		Urea nitrogen		Ammonia nitrogen			Preformed creatinine nitrogen		Creatinine nitrogen			Uric acid nitrogen			Total amino acid nitrogen		
				Daily, gm	Increase, per cent of glycine nitrogen	Daily, gm	Per cent of total nitrogen	Daily, gm	Per cent of total nitrogen	Change, per cent	Daily, gm	Per cent of total nitrogen	Daily, gm	Per cent of total nitrogen	Change, per cent	Daily, gm	Per cent of total nitrogen	Change, per cent	Daily, gm	Per cent of total nitrogen	Change, per cent
Subject 1																					
I ¹	4	0	12 20	11 54	68	9 86	85	0 41	3 6	0	0 43	3 5	0 17	1 5	0 18	1 6	+33	0 17	1 5	247	
II ^{1a}	1	7 40	12 20	16 58		13 98	84	0 41	2 5		0 40	2 0	0 24	1 4	0 24	1 4	+41	0 59	3 6	141	
b	6	7 40	12 20	19 70	110	17 29	88	0 62	3 1	51	0 44	2 2	0 25	1 3	0 22	1 1	+47	0 41	2 2	124	
c	4	7 40	12 20	18 61	96	16 89	91	0 60	3 2	46	0 45	2 3	0 25	1 3	0 19	1 0	+47	0 38	2 0	124	
Average, II ¹	11	7 40	12 20	19 02	101	16 84	89	0 60	3 2	46	0 44	2 2	0 25	1 3	0 21	1 1	+17	0 41	2 2	141	
Subject 2																					
I ²	4	0	8 20	11 55		9 55	83	0 49	4 2		0 55	6 8	0 04	0 78	0 15	1 3		0 21	1 8	90	
II ^{2a}	3	5 56	8 29	16 10	82	11 44	71	3 29	20 4	+571	0 53	3 1	0 13	0 81	0 19	1 2	+44	0 40	2 5	71	
b	3	5 56	8 29	16 08	81	12 34	77	2 23	13 8	+355	0 54	3 2	0 21	1 30	0 17	1 1	+133	0 36	2 2	76	
c	6	5 56	7 62	16 04	81	12 88	80	0 95	5 9	+94	0 53	4 0	0 18	1 12	0 17	1 1	+100	0 37	2 3	76	
Average, II ²	12	5 56	7 96	16 07	81	12 39	77	1 86	11 5	+281	0 54	4 1	0 17	1 06	0 17	1 1	+89	0 37	2 3	76	

Subject 1 Increased excretion of nitrogen = 101 per cent of increased intake of nitrogen

Sum of increase in urea, ammonia, creatine, uric acid, amino acid = 101 per cent of increased intake of nitrogen

Subject 2 Increased excretion of nitrogen = 81 per cent of increased intake of nitrogen

Sum of increase in urea, ammonia, creatine, uric acid, amino acid = 80 per cent of increased intake of nitrogen

have been grouped arbitrarily into three subperiods during each of which the daily values remained relatively constant

The nitrogen distribution during the control periods was apparently normal for each subject, except for the presence of some creatine, a condition occasionally encountered in myasthenia gravis¹ During the periods of administration of glycine there occurred in subject 1 a marked temporary retention of nitrogen for the first day or two This was later excreted, however, and the average increase in the urinary nitrogen for the entire period was equivalent to 101 per cent of the nitrogen ingested as glycine For subject 2, the increase in the nitrogen of the urine was equivalent to only 81 per cent of the glycine ingested

The increased urinary nitrogen was largely in the form of urea Changes in the other nitrogenous constituents were relatively small and accordingly the nitrogen partition products remained essentially normal For subject 1, the average change in urea accounted for 93 per cent of the increased nitrogen, and that of ammonia for 2.6 per cent In the urine specimens of subject 2 the urea appeared to be markedly unstable,* and the change in urea accounted for only 63 per cent of the increased nitrogen, while the ammonia was unusually high and accounted for an average of 30 per cent of the increased nitrogen Thus, for both subject 1 and subject 2, the changes in urea plus ammonia accounted for substantially the same fraction of the increased nitrogen in the period when glycine was being given

The excretion of creatinine during the periods of administration of glycine was unchanged as compared with the excretion during the control periods Creatine, however, was excreted in definitely increased quantities This response to glycine we have considered in detail in previous publications^{1,2} A slight increase in the excretion of uric acid by both subjects was observed This was characterized by an initial increase followed by a gradual return to approximately the levels of the control periods A marked increase occurred in the excretion of total amino acids by both subjects Analyses for amino acids by Folin's⁷ method indicated that the free amino acids accounted for only about 40 per cent of this increase It was found later, however, that the permutit sample used in these determinations absorbed both ammonia and amino acids, and subsequent analyses by the method of Van Slyke have shown that practically all of the increase in excretion of amino acid during the administration of glycine is in the free amino acid fraction Relative to the amounts of glycine involved, the increases were small, only about 3 per cent of that ingested

The increased excretion of urea, ammonia, creatine, uric acid and amino acids in the periods of administration of glycine accounted satisfactorily for all of the extra nitrogen appearing in the urine, 100 per cent and 99 per cent for subjects 1 and 2, respectively The average undetermined nitrogen fractions, therefore, were not appreciably altered by glycine, and

* We have encountered this same type of instability in the urine of several other subjects who were taking glycine

TABLE III
Sulphur Partition Products and Inorganic Phosphate Excretion in the Urine before and during the Administration of Glycine

Period	Days	Glycine nitrogen	Total sulphur			Neutral sulphur			Conjugated sulphur			Inorganic sulphur			Inorganic phosphate	
			Intake	Daily, gm	Change, per cent	Daily, gm	Change, per cent	Per cent of total sulphur	Daily, gm	Change, per cent	Per cent of total sulphur	Daily, gm	Change, per cent	Per cent of total sulphur	Daily, gm	Change, per cent
Subject 1																
I ¹	4	0	0.891	0.770	- 3.9	0.102		13.2	0.054		7.0	0.615		79.9	0.81	
II ^{1a}	1	7.40	0.891	0.740	+ 10.5	0.096	- 5.9	13.0	0.066	+ 22.2	8.9	0.579	- 5.9	78.2	1.02	+ 25.9
b	6	7.40	0.891	0.851	+ 3.0	0.127	+ 25.5	14.9	0.054	0.0	6.3	0.670	+ 8.9	78.9	0.86	+ 6.2
c	4	7.40	0.891	0.793	+ 38.2	0.141	+ 38.2	17.8	0.047	- 13.0	5.9	0.606	- 1.5	76.4	0.84	+ 3.7
Average, II ¹	11	7.40	0.891	0.820	+ 6.5	0.129	+ 26.5	15.7	0.053	- 1.9	6.5	0.638	+ 3.7	78.0	0.86	+ 6.2
Subject 2																
I ²	4	0	0.695	0.806		0.097		12.0	0.016		2.0	0.693		86.0	1.01	
II ^{2a}	3	5.56	0.705	0.807	+ 0.1	0.130	+ 34	16.0	0.032	+ 120	4.0	0.646	- 6.8	80.0	0.98	3.0
b	3	5.56	0.705	0.766	- 5.0	0.103	+ 6	13.4	0.040	+ 150	5.2	0.624	- 10.0	81.5	0.93	7.9
c	6	5.56	0.664	0.757	- 6.1	0.122	+ 26	16.1	0.047	+ 194	6.2	0.587	- 15.3	77.5	0.90	10.0
Average, II ²	12	5.56	0.685	0.772	- 4.3	0.119	+ 22	15.4	0.042	+ 165	5.4	0.611	- 11.8	79.1	0.93	7.9

it appears that no very large amounts of unknown nitrogen-containing substances were formed, although the possibility of alterations in the character of the undetermined nitrogen fraction cannot be excluded

In table 3 the data for the sulphur partition products of the urine, and for the excretion of inorganic phosphate, are presented in a form similar to that employed in table 2. The excretion of total sulphur and inorganic sulphate by subject 1 during administration of glycine was roughly parallel to the excretion of nitrogen, while there was no change in the conjugated sulphate fraction. There was a small decrease in the excretion of total sulphur by subject 2, with a more marked decrease in the inorganic fraction. At the same time the conjugated sulphates increased considerably over the rather unusually low value of the control period. There were rather substantial increases in the excretion of neutral sulphur by both subjects. The excretion of phosphate by subject 1 was markedly increased on the first day of administration of glycine, but later returned to a level only slightly above that of the control period. On the other hand, the excretion of phosphate in the urine by subject 2 progressively decreased during the period of administration of glycine.

COMMENT

On the basis of these results it seems impossible to conclude that there is any particular metabolic abnormality in myasthenia gravis. The two subjects presented certain marked differences, particularly in respect to the balance studies. These may be ascribed to their widely different clinical conditions, and it may be suggested that the results of previous attempts to demonstrate metabolic abnormalities probably have been determined entirely by the condition of the patient when studied. The tendency toward a relative negative potassium balance observed in subject 1 may possibly have some significance, in view of the recent reports of Laurent and Waltham¹² that large doses of potassium salts afford temporary relief in this disease.

The response of the two subjects to administration of glycine, as shown by the nitrogen and sulphur partition products in the urine, was, on the whole, quite similar. Aside from the increased excretion of urea, ammonia, and amino acids there were small but definite changes in the excretion of creatine, uric acid, and neutral sulphur. This suggests that glycine exerts some influence on the so-called "endogenous" metabolism. On the other hand, the changes appeared at variable times after the beginning of administration of glycine, and did not run parallel courses throughout the experiments, so that it seems useless to attempt interpretations until many more data have been accumulated.

SUMMARY

In complete balance studies of two subjects who had myasthenia gravis, during which the nitrogen and sulphur partition products of the urine were also determined, it was not possible to demonstrate any metabolic abnormality which could be considered characteristic of the disease.

The type of balance obtained appeared to depend largely on the condition of the subject. One subject was in approximate equilibrium as regards the nitrogen, sulphur and inorganic constituents. The administration of glycine to this individual had remarkably little influence on the various balances. The second subject was in markedly negative nitrogen balance throughout the experiments although, during the administration of glycine, the large net loss of nitrogen was somewhat decreased. Glycine exerted little influence on the balance of the other constituents.

The extra nitrogen appearing in the urine during the administration of glycine was chiefly in the form of urea and ammonia. The urinary excretion of creatine, uric acid, amino acids, and neutral sulphur was also slightly but definitely increased.

BIBLIOGRAPHY

- 1 ADAMS, M, POWER, M H, and BOOTHBY, W M. Chemical studies in myasthenia gravis, *ANN INT MED*, 1936, ix, 823-833
- 2 ADAMS, M, POWER, M H, and BOOTHBY, W M. Influence of glycine on excretion of creatine and creatinine, *Am Jr Physiol*, 1935, cxv, 596-610
- 3 BARBER, H H, and KOLTHOFF, I M. A specific reagent for the rapid gravimetric determination of sodium, *Jr Am Chem Soc*, 1928, l, 1625-1631
- 4 BUTLER, A M, and TUTHILL, E. An application of the uranyl zinc acetate method for determination of sodium in biological material, *Jr Biol Chem*, 1931, xciii, 171-180
- 5 FISKE, C H, and SUBBAROW, Y. Colorimetric determination of phosphorus, *Jr Biol Chem*, 1925, lvi, 375-400
- 6 FOLIN, O. On the determination of creatinine and creatine in urine, *Jr Biol Chem*, 1914, xvii, 469-473
- 7 FOLIN, O. Colorimetric determination of amino-acid nitrogen in normal urine, *Jr Biol Chem*, 1922, li, 393-394
- 8 FOLIN, O, and WU, H. Revised colorimetric method for determination of uric acid in urine, *Jr Biol Chem*, 1919, xxxviii, 459-460
- 9 FOLIN, O, and MARENZI, A D. The preparation of uric acid reagent completely free from phenol reagent, *Jr Biol Chem*, 1929, lxxxiii, 109-113
- 10 HUBBARD, R S. Determination of inorganic sulfate in serum, *Jr Biol Chem*, 1930, lxxxviii, 663-668
- 11 KOCH, F C. Modified Van Slyke amino nitrogen apparatus, *Jr Biol Chem*, 1929, lxxxiv, 601-603
- 12 LAURENT, L P E, and WALTHER, W W. Influence of large doses of potassium chloride on myasthenia gravis, *Lancet*, 1935, i, 1434-1435
- 13 ROSSENBECK, H. Zur Frage der Veraschung von biologischem Material, *Biochem Ztschr*, 1929, ccviii, 428-442
- 14 SHERMAN, H C. Methods of organic analysis, 1920, Macmillan Company, New York, pp 301-303
- 15 TISDALE, F F, and KRAMER, B. Methods for direct quantitative determination of sodium, potassium, calcium and magnesium in urine and stools, *Jr Biol Chem*, 1921, lviii, 1-12
- 16 VAN SLAKE, D D. Improved methods in the gasometric determination of free and conjugated amino-acid nitrogen in the urine, *Jr Biol Chem*, 1913, vi, 125-134
- 17 VAN SLAKE, D D. Determination of urea by gasometric measurement of carbon dioxide formed by the action of urease, *Jr Biol Chem*, 1927, lxxviii, 695-723
- 18 VAN SLAKE, D D, and CULLEN, G E. A permanent preparation of urease, and its use in the determination of urea, *Jr Biol Chem*, 1914, vi, 211-228

THE TREATMENT OF ADDISON'S DISEASE WITH SODIUM COMPOUNDS, WITH THE REPORT OF ONE CASE AND THE SUMMARIES OF ELEVEN OTHER COLLECTED CASES THUS TREATED *

By EDWARD C REILNSTEIN, M D , F A C P , and EDWARD C RLIFENSTEIN, JR , M D , *Syracuse, N Y*

THE treatment of Addison's disease has undergone a marked change in the last five years. Ever since 1855, when Addison first described the insufficiency disease of the suprarenal cortex that now bears his name, investigators have been trying to devise an adequate treatment for this condition.

MUIRHEAD REGIME

Previous to 1930, physicians relied chiefly on the Muirhead regime,¹ which consisted of administering epinephrine by mouth, by rectum, and subcutaneously at frequent intervals and up to the patient's tolerance, together with "desiccated cortex" by mouth, 10 to 15 grains daily. Results from this regimen were observed in 10 to 20 per cent of the cases.

CORTICAL HORMONE THERAPY

In 1930 Swingle and Pfiffner² announced a potent extract of the adrenal cortex, and with Hartman³ and others developed the cortical hormone substitution therapy. This treatment has been of considerable value in meeting the critical episodes of the disease, and in restoring many invalids to a reasonable degree of health. Snell,⁴ however, in reporting 46 cases treated with the extract, pointed out that the patients have not been restored to full efficiency and their lives have not been indefinitely prolonged, consequently the therapy can not be considered entirely satisfactory. In addition, the cost of the cortical extract makes this form of treatment prohibitive at present.

SODIUM COMPOUND THERAPY

Recently sodium compounds have been found to have a definite place in the treatment of Addison's disease. G N Stewart⁵ in 1924 paved the way for this discovery by explaining the cause of previous discrepancies in the results of experimental adrenalectomy, as due to such factors as shock resulting from poor quality surgery, the nature and duration of the anesthesia, undue loss of heat, and lack of attention to the nutritive state of the animals before and after the operations. He found that the operations had

* Received for publication October 1, 1935.

From the Medical Service of the University Hospital, and the Department of Medicine of the Syracuse University College of Medicine.

not been performed in such a way as to insure complete removal of the glands, and in almost all instances the extirpation had not been controlled by adequate postmortem search for remaining adrenal tissue or accessory gland substance. Stewart pointed out that animals surviving only a few days after adrenalectomy cannot rightfully be assumed to be suffering from adrenal insufficiency.

Following such caustic criticism, investigators began to control their work more carefully, and results appeared which could be confirmed at other hands. Stewart himself, with Rogoff,⁶ was able to keep dogs alive for sufficient periods to rule out the question of shock, and among other observations noted that the use of Ringer's solution with dextrose intravenously, in seven out of 36 bilaterally adrenalectomized dogs, increased the span of life considerably and ameliorated the symptoms. In 1926 Banting and Garms⁷ from their experience with 56 dogs found that saline increased the length of life. Lucas⁸ noted a fall in the chlorides of the blood in bilaterally supra-renalectomized dogs. In 1927 Corey⁹ reported that oral administration of large quantities of fluid to bilaterally adrenalectomized cats prolonged life, and that solutions of certain substances, notably glucose and sodium chloride, were more effective. Zwerner¹⁰ also found an amelioration of symptoms with administration of fluid following bilateral adrenalectomy. All of these investigators failed to realize the significance of the sodium ion.

The first significant step in the discovery of the value of sodium salts seems to have been taken by Baumann and Kurland¹¹ in 1927. Their adrenalectomized cats lived five to six days, consequently, they were able to compare the blood chemistry of such animals with a normal unoperated group. In the adrenalectomized animals the sodium of the blood plasma fell from a normal of 375 milli-equivalents per liter to 320, or a loss of 15 per cent, while the chlorides fell from 415 to 378, or a loss of 9 per cent. At the same time there was an increase of 42 per cent in the potassium of the plasma.

Marine and Baumann¹² studied the effect of various solutions on the length of life of bilaterally adrenalectomized cats. Their series included 167 cats, of which 101 were considered sufficiently free from possible complicating factors to be included in tables of analysis. They found that the animals would live five days without any medication, 10 days if cortical extracts were injected, and 15 days if a daily injection of 50 c.c. of normal saline was given intraperitoneally. Concentrated saline shortened the period of life, and hence it was assumed that water to bring the saline to a physiological solution was necessary. However, diuretic solutions, such as isotonic glucose, failed to prolong life materially, and therefore the value of the treatment could not be attributed to the fluid alone. Ringer's solution, physiological saline, sodium acetate, and sodium glycono-phosphate were found to have about the same effect, and consequently it appeared that the sodium and not the chloride is important. They felt their evidence indicated a specificity in the action of the sodium ion.

The next and most important step was taken by R F Loeb¹³ who made a complete analysis of the inorganic bases of the blood plasma of patients with severe Addison's disease. The normal level of sodium in the blood plasma he assumed to be about 138 milli-equivalents per liter (317.4 mg per cent), which corresponds well with the figure of 140 milli-equivalents given by Butler and Luthill¹⁴. Loeb found the chief abnormality in his patients to be in the sodium content, which in three cases was respectively 109, 131, and 108 milli-equivalents per liter (250, 301 and 248 mg per cent), a definite decrease in each instance. The potassium content was very high, in two cases being 8.7 and 7.1 milli-equivalents per liter (34 and 27.7 mg per cent), the normal being 4.8 (18.7 mg per cent), the chlorides being reduced to 70 and 73 (248 and 259 mg per cent), the normal being 103.15 (365.6 mg per cent).

Working with Atchley, Benedict, and Leland, Loeb then made studies of the inorganic base balance in three dogs before and after adrenalectomy¹⁵. The removal of only one adrenal gland produced no change in any of the dogs, but the removal of the remaining gland caused a decrease in the sodium of the blood-serum from 147 to 126 milli-equivalents per liter, while the potassium level was slightly elevated. At the same time the sodium in the urine increased markedly, and the chlorides were increased also, but not to the same extent as the sodium.

These observations were confirmed by Harrop, Soffer, Ellsworth, and Trescher¹⁷. They produced bilateral adrenalectomy in dogs, and then maintained them in a state of normal health with cortical extract until the animals had fully recovered from the effects of the operation. Upon ceasing the extract, the dogs had a characteristic alteration in the blood and urinary findings: the plasma concentration increased, the sodium concentration in the plasma decreased, and with it the chlorides and part of the body water, while the potassium and magnesium were increased. At the same time within 48 to 72 hours the sodium, chloride, and water excretion in the urine was much increased. When the extract was resumed, there was retention of sodium, and with it chloride and water in the body in excess of the excretion. This continued until the animals returned to normal. In another series of dogs, the extract was continued, and the animals fed a salt-poor diet, following which insufficiency appeared. The dogs were returned to a normal state by injections of salt alone. These same animals were then placed on the identical salt-poor diet, with 1.5 grams of salt added, and no evidence of insufficiency appeared. From this, these investigators suggested that the dosage of the cortical extract may be reduced to a fraction of its original amount by using a high salt diet with it.

The proof of the connection between sodium and dysfunction of the adrenal cortex was finally established by Loeb,¹⁸ who gave a patient salt and found marked improvement. The patient, a woman, on admission had a classical picture: progressive weakness, loss of appetite and weight, increasing pigmentation of skin, nipples, and buccal membranes, mild sec-

ondary anemia and a blood pressure of 90 systolic and 60 diastolic. At that time the sodium concentration of her blood was 123 milli-equivalents per liter (284 mg per cent), normal being 138 (317.4 mg per cent). One week later the sodium had fallen to 107 (247.9 mg per cent), and the woman was in a much more severe condition, with profound exhaustion, slight dyspnea, increasing nausea, and recurrent vomiting. The chlorides had decreased proportionally, the potassium had risen and the blood pressure was 65 systolic and 48 diastolic. She was given 9.5 grams of sodium chloride daily by proctoclysis, and 5 grams a day by mouth in capsules. Within four days the clinical improvement was so striking that rectal administration was stopped, and the convalescence maintained with five to seven grams of salt a day in addition to a liberal amount in the diet. She continued to gain, and was discharged on a regular diet plus one and a half teaspoonfuls of salt daily.

She remained well for five months, gained seven pounds, and was able to do her housework. Her sodium level was then entirely normal. At this stage she developed some edema under the eyes, and was advised to take a low salt diet, containing about 2 grams of sodium chloride. Two days later she was so weak she had to go to bed, and for the next five days became progressively weaker and vomited at frequent intervals. She was readmitted to the hospital and was found to have a low serum sodium reading of 126 milli-equivalents (291.6 mg per cent), with a low chloride and a high potassium level. She was immediately given seven grams of sodium chloride by mouth, and a rectal drip of 200 c.c. of physiological saline every four hours. No other treatment was used. Within three days she had improved to such a remarkable extent that the rectal instillations were stopped, and she was discharged on the eighth day in excellent health, having gained four pounds. Her blood chemistry was again entirely normal. Subsequently Loeb¹⁹ reported that more than two years after the first admission the same patient continued to maintain her improvement, and complained only of usually feeling cold and of tiring rather easily. On her own initiative she had increased the sodium chloride to 15 grams daily. The blood sodium level and the blood pressure were still normal, with the pigmentation slightly decreased.

Loeb, Atchley, Gutman, and Jillson²⁰ have repeated this experiment on another patient. She was at first allowed to eat an ordinary diet with as much salt as she wanted. On this she was able to be up in the ward, although she complained of nausea, occasional abdominal pain, and slowly increasing weakness. She was then put on a low salt diet, and immediately became worse, with dizziness, nausea, and marked prostration, so that at the end of the first day she had to stay in bed. The sodium level in the serum, which had been falling gradually during the normal diet, took a decided drop after 48 hours on the low salt diet. The addition of excess salt to the diet led to rapid recovery, and the patient was able to get up in

two days, and leave the hospital in five, when the sodium had risen again to normal. She was instructed to continue oral salt in addition to a highly seasoned diet.

These observations have been confirmed by Hariop, Weinstein, Soffer, and Trescher²¹. They found that with a high salt diet they could diminish the potency of the cortical extract to such an extent that it would not have any effect in prolonging the lives of adrenalectomized dogs, and yet the patients remained symptomless, and continued to gain weight and strength on it for nine months. However, when the extract was replaced with a 'hypo' of sterile water in one patient, there was a relapse after six weeks. The patient improved again when put back on the low potency extract and the high salt diet. The authors then placed the patient on a low salt diet, while continuing the extract, and within two days the patient lost appetite and complained of great weakness. The sodium and the chloride levels in the blood serum were considerably lowered. When treated with intravenous saline the patient gradually improved, and 22 days after the start of the experiment, the blood findings were again essentially normal. The same workers had similar results in another case, with a definitely low sodium level, which was restored to normal after one week on a high salt diet and oral salt. The authors then removed the extract entirely from four patients, and placed them on a highly seasoned diet with additional salt. All continued to feel strong, were found to tire less easily, and were relieved of the persistent recurring nausea and vomiting that had been present before treatment. There was a definite gain in weight in one patient.

In January 1934, Sears²² in England studied a case of Addison's disease of seven years' duration. He found the blood sodium level to be very low on admission. After one week on a regular diet and sodium chloride by mouth daily, the sodium level had risen to well above normal, and there was marked subjective improvement. The patient was discharged on a maintenance dosage of salt. Shortly after, Snell²³ at the Mayo Clinic reported a case of Addison's disease of exceptionally long duration (17 years). The extended course of the disease seemed to be partially attributable to the fact that the patient of his own accord had been using salt excessively for the past few years. The patient had an acute episode in May 1934, and was treated with cortical extract and sodium chloride daily with marked clinical improvement but no change in the electrolytes of the blood. Howell²⁴ in England in May 1934 found the blood sodium level in a case of Addison's disease of six months' duration to be only slightly decreased on admission. He placed the patient on sodium chloride and reported a dramatic effect in 24 hours, with the patient changed from a listless, apathetic invalid to an alert individual sitting up in bed, reading. When the salt dosage was cut in half without the patient's knowledge, anorexia, weakness and vomiting occurred within one week. The patient was restored to normal by returning to the original dosage.

THE SALT-POOR DIET CONFIRMATORY TEST FOR ADDISON'S DISEASE

Harrop, Weinstein, Soffer, and Trescher²¹ suggested that the withdrawal of salt from the diet should be used to confirm the presence of Addison's disease. They recommended that this test should be used only if large amounts of potent cortical extract are available, as the condition of the patient may be very alarming after 24 to 48 hours on a low salt diet. If, however, the patient is no worse for the deprivation of salt, it must be considered extremely unlikely that he has Addison's disease.

Nettrour and Ryncarson²⁵ at the Mayo Clinic made use of this test in the case of a 21 year old boy with a typical history of nausea, vomiting, and extreme weakness and fatigue, but without the characteristic pigmentation. On admission the blood pressure was 78 systolic and 52 diastolic while reclining, the sodium and chloride levels were considerably decreased, the basal metabolic rate was subnormal, and there was a mild secondary anemia. The patient was placed on a salt-poor diet for five days, with a marked increase in the severity of the nausea, vomiting and prostration, while the chloride fell to a very low level. Intravenous physiologic saline, cortical extract, and sodium chloride by mouth daily restored the patient to normal in four days, the blood electrolytes returning to approximately normal level. The therapeutic test of the salt-poor diet as an aid in the diagnosis of Addison's disease was therefore entirely successful.

Touw and Noordhoek Hegt²⁶ in Holland observed clinical manifestations and blood chemistry of two patients with Addison's disease during periods of normal, salt-poor, and excessive salt diets. There was a noteworthy parallelism between the clinical improvement of the patients and the rise of the sodium content of the blood after the oral administration of 20 to 35 grams of sodium chloride daily.

Loeb^{19b} recently reported a case clearly demonstrating the serious consequences that may follow the salt-poor diet test. His patient after four days of salt deprivation suddenly developed shock, although only a relatively small decrease of the sodium level was present, and then continued in an alarming state in spite of large amounts of cortin, fluid and salt. Hypoglycemia, ketosis, and dehydration were found to be complicating the picture, and were combated for a week with a continuous infusion of salt and dextrose before the patient was considered out of danger. Loeb says significantly, "It is unfortunate that a diagnostic procedure so highly specific as is salt withdrawal in Addison's disease should be attended by such grave consequences to the patient."

ANTERIOR LOBE PITUITARY EXTRACT THERAPY

Wilder²⁷ at the Mayo Clinic in November 1934 reported two cases of Addison's disease treated with cortical extract, sodium chloride by mouth, and anterior lobe pituitary extract. He pointed out that the majority of the patients with Addison's disease required a larger than normal supply

of sodium chloride even when receiving adequate amounts of cortical extract, and suggested a secondary deficiency in the hormone of the anterior lobe of the pituitary body because of changes in the basophile and chromophile cells of that gland found in cases of Addison's disease²⁶ He showed, as had previous workers, that the patients could be restored to approximately normal health with cortical extract and oral sodium salts, and that relapses occurred when either of these forms of medication was discontinued He found, however, that when anterior lobe pituitary extract was given in addition to the cortical extract and the salt, the patients felt stronger and were considerably less sensitive to the deprivation of the sodium chloride Wilder suggested that this sensitiveness may be due to secondary insufficiency of the anterior lobe of the pituitary associated with the adrenal insufficiency in Addison's disease

THE SPECIFICITY OF THE SODIUM ION

It was pointed out by Loeb and his associates²⁰ that there is apparently a specific relation between the sodium ion and the adrenal glands He suggested that these organs play an important rôle in the regulation of the sodium metabolism in the normal body, analogous to that of the parathyroid with calcium and phosphorus, and that the sodium depletion occurring in adrenal insufficiency is dependent therefore on a disturbance of this normal function There is loss of sodium without a change in potassium excretion, whereas in other clinical states with base loss the sodium depletion is accompanied by a parallel loss of potassium, as in starvation,²⁰ diabetes,³⁰ ammonium chloride acidosis,³¹ and severe diabetic glycosuria³⁰ Zwemer³² in 1934 reviewed the experimental data and similarly concluded that the adrenal cortex has a regulative effect on the salt and water metabolism of the cell

The experimental evidence of the specificity of the sodium ion in adrenal cortex insufficiency can be found in the work of Marine and Baumann¹² already cited They showed that the various isotonic fluids that were effective in prolonging the life of bilaterally adrenalectomized cats contained only the sodium ion in common, and that isotonic solutions such as glucose failed to prolong life materially

Clinically this point was clearly demonstrated in the case reported in March 1935 by Blankenhorn and Hayman³³ They treated a case of Addison's disease of three months' duration with oral sodium chloride daily, and obtained subjective and clinical improvement The blood sodium content and the blood pressure rose from low levels to approximately normal The provocative salt-poor diet test readily confirmed the diagnosis When the salt medication was discontinued the patient promptly had a relapse with weakness, anorexia, nausea and irrationality, and the blood chlorides again fell to a low level The patient failed to respond to cortical extract intramuscularly and intravenously, and it was only by giving saline intra-

venously that he was saved from imminent disaster. The patient was then returned to oral salt daily, and remained in good health for several weeks. At that point it was decided to test the specificity of the sodium ion. Accordingly the sodium chloride was replaced by other chloride salts. In three days the patient developed abdominal pain, nausea, and vomiting. Intravenous saline and oral sodium chloride then restored the patient to normal, and after two weeks the patient was in excellent health. A mixture of sodium salts, the sulphate, the phosphate, and the bicarbonate, containing an amount of sodium equal to that previously given, was then substituted. This was given for 17 days without any discomfort, with the patient continuing apparently well. The specificity of the sodium ion was thus clearly demonstrated. The patient was put back again on sodium chloride medication, and after two weeks in spite of 16 grams daily, developed a severe crisis complicated by bronchopneumonia and expired.

We obtained similar results with the case herein reported. After demonstrating the improvement of the patient on sodium chloride and, after confirming the diagnosis with the salt-poor diet test, we restored the patient to normal by oral sodium chloride and then placed him on a mixture of sodium biphosphate and sodium bicarbonate. This sufficed to maintain excellent health according to all tests, for over two weeks, again demonstrating the specificity of the sodium ion.

THE PROLONGATION OF LIFE

The question of how much prolongation of life can be expected from these therapeutic advances naturally arises. Experimental adrenalectomized animals apparently can be kept alive almost indefinitely with injections of potent cortical extract. The effect of sodium salts alone on adrenalectomized animals has been studied by several investigators.

Rubin and Krick³⁴ found that untreated bilaterally operated rats could not be kept alive over 10 days, but if while exhibiting symptoms of severe insufficiency, they were given a special solution of calcium, magnesium, sodium and potassium chlorides, they could be restored to normal in four to five hours, and could be kept alive over four months. Gaunt, Tobin and Gaunt³⁵ in October 1934 studied another series of bilaterally adrenalectomized rats. Only four of the adult control series of 24 survived over 30 days. The experimental series of 23 rats was given a sodium chloride solution for 30 days following the operation. Five animals succumbed 14 to 25 days after operation with typical symptoms of adrenal insufficiency, six animals survived the treatment period and were in good health, but when returned to normal diet and distilled water, developed adrenal insufficiency and died in 10 to 15 days, 12 animals, approximately 50 per cent, survived in good health and remained well afterwards on normal diet and distilled water. When killed and autopsied eight or more weeks later, seven of these were found to have accessory glands.

Swingle, Piffner, Vais, and Parkins²⁶ fed sodium chloride to the point of tolerance to seven bilaterally adrenalectomized dogs while withholding cortical extract. Three animals remained free from symptoms for 14 days, one for 12 days, one 21 days, one 19 days, and one 50 days. Salt was withdrawn from the diet of the long surviving animal on the fiftieth day, and four days later the dog exhibited severe symptoms of insufficiency. They found that the interval between cessation of extract injections and development of adrenal insufficiency was somewhat prolonged by the feeding of sodium chloride, but concluded that the sodium chloride and water could not be regarded as an effective substitute for the cortical hormone in the bilaterally adrenalectomized dog since it was necessary to inject cortical extract to save the animals when they sooner or later developed severe symptoms.

Zwemer³² reported similar results on a series of completely adrenalectomized cats. The average length of life in the control group was 10 days, while the average survival period of the experimental animals, which were treated with a number of different sodium compounds, was 18.4 days.

It appears from this experimental work, therefore, that as far as animals are concerned, the administration of sodium compounds alone without cortical extract in adrenal insufficiency will increase the span of life to some degree but not indefinitely, and that sodium salts are therefore not substitutes for the cortical extract. In some animals, however, the presence of accessory adrenal glands (as in rats) makes the adrenal insufficiency only a relative matter, and in such cases the sodium compounds, by delaying the appearance of the symptoms, will allow time for this accessory gland substance to hypertrophy sufficiently to permit the animals to survive indefinitely.

Clinically, however, sodium medication alone seems to have been more successful. Loeb's¹⁹ original classic patient is still feeling well after two years on salt, and of the eight patients he has studied since 1932, six are still alive in fairly good health. Our patient has been in good health for over six months, and others have reported similar results. Harrop and associates³¹ kept four patients symptomless for nine months with sodium medication and a cortical extract that was too weak to prolong the lives of adrenalectomized dogs. The death of Blankenhorn and Hayman's³³ patient in spite of 16 grams of sodium chloride daily is less encouraging, although a bronchopneumonia complicated the picture. The fact that Snell's²³ patient had been consuming salt excessively for several years before receiving medical attention may partially explain the unusually long duration of that case. Whether sodium salts alone will suffice to keep patients alive indefinitely remains to be seen, and depends, perhaps, on the hypertrophy of the remaining undiseased portions of the adrenal glands in the individual case.

THE DOSAGE OF SODIUM CHLORIDE

In treating Addison's disease with sodium chloride it is recommended that the dosage of salt be large—10 to 15 grams a day.³⁷ Loeb²⁰ treated a

case with 20 grams daily, and the Holland investigators²⁶ have used as much as 35 grams daily. Divided doses seem to be most suitable, given either in milk, capsules, or tablets. We have had considerable success with plain uncoated one gram tablets. Enteric-coated tablets should be used with caution, as the coating may fail to dissolve.²⁵

In some patients it may not be possible to maintain health without the use of cortical extract, and others at first maintained satisfactorily on salt alone may later need the glandular preparation, but the dose of the extract in such cases is likely to be much smaller than if no additional salt were given. The extract of the anterior lobe of the pituitary should be tried in addition in refractory cases, as suggested by Wilder.²⁷

CASE REPORT

A G, aged 39, an Italian male, was admitted to the University Hospital, December 9, 1934, complaining of nausea, vomiting, chills, fever, and extreme weakness of 48 hours' duration.

His family history failed to reveal any hereditary tendencies. His past history showed pneumonia at 17 years of age, malaria at 24 years of age, and an appendectomy at 30 years of age. Otherwise he had been well until the present illness. He denied venereal disease. The patient has lived in the United States for 11 years, and has a wife and four children, living and well.

The patient stated that he had suffered from a similar attack in May 1932, which confined him to his bed for one month. Shortly after the onset of this original attack he noticed increasing prostration and darkening of his skin. Except for these two manifestations his condition remained unchanged until June 1934 when he was again confined to his bed with extreme weakness, and remained prostrated throughout the month of July. In August, notwithstanding the increasing fatigue, he worked as a laborer for the County Welfare Organization, but found the exertion required a great effort. Finally he became so weak that he could not continue. On December 8, 1934, the day before admission to the hospital, he suddenly developed an acute episode consisting of bowel movements every 20 minutes associated with frequent attacks of vomiting, severe chills, marked dyspnea, excessive perspiration, and generalized aches and pains.

The patient was admitted to the hospital by ambulance, acutely ill and in a state of collapse. The significant findings on physical examination were extreme prostration, emaciation and dehydration, marked pigmentation of the face, hands, axillae, elbows, knees, buccal membrane, and anal margin, feeble, distant heart sounds, blood pressure 58 systolic and 36 diastolic, flat abdomen, temperature elevated to 100 degrees, and radial pulse of 80 beats per minute. A diagnosis of Addison's disease was made, and a clysis of glucose and normal saline was given immediately. Laboratory studies on admission revealed hemoglobin 110, red cells 5,400,000, white cells 8,000, non-protein nitrogen 75 mg per cent, blood sugar 95 mg per cent, chlorides 335.1 mg per cent, serum protein 6.1, albumin 5, globulin 1. The urine contained acetone, diacetic acid, albumin, red cells, and granular and hyaline casts. Roentgen-ray evidence of an old tuberculous lesion affecting the upper right lung field was reported, but no calcified areas could be visualized in the kidney regions.

For the following six days he was given frequent clyses of glucose and normal saline, with slight improvement at first so that there was less nausea, vomiting, and restlessness. During this interval the blood pressure rose temporarily to 86 systolic and 58 diastolic, and then fell steadily to 73 systolic and 50 diastolic, the non-protein nitrogen remained elevated and the blood chlorides continued below normal. On

the night of December 17, eight days after admission, the patient became irrational, got out of bed, and attempted to get into bed with another patient. This episode occurred after a restriction of fluids. The following day two grams of sodium chloride were given every four hours with decided improvement, so that within 24 hours the patient was cooperative and cheerful. The non-protein nitrogen was then 46, and the blood pressure 89 systolic and 57 diastolic, with marked improvement in the condition of the patient, and at the end of 72 hours he was sitting up in bed reading. The sodium chloride was increased to 15 grams daily, whereupon the non-protein nitrogen became normal and the blood chlorides increased to 366.6 mg per cent.

One week later the patient was in excellent health, feeling better than he had for many months. At this point it was decided to confirm the diagnosis with a salt-poor diet. He was placed on this regime and all other medication was withheld. Within 12 hours he complained of increasing fatigue, which was followed by extreme restlessness and marked prostration. His sufferings excited the sympathy of a fellow ward patient who gave him a salt shaker when the attendants were not watching.

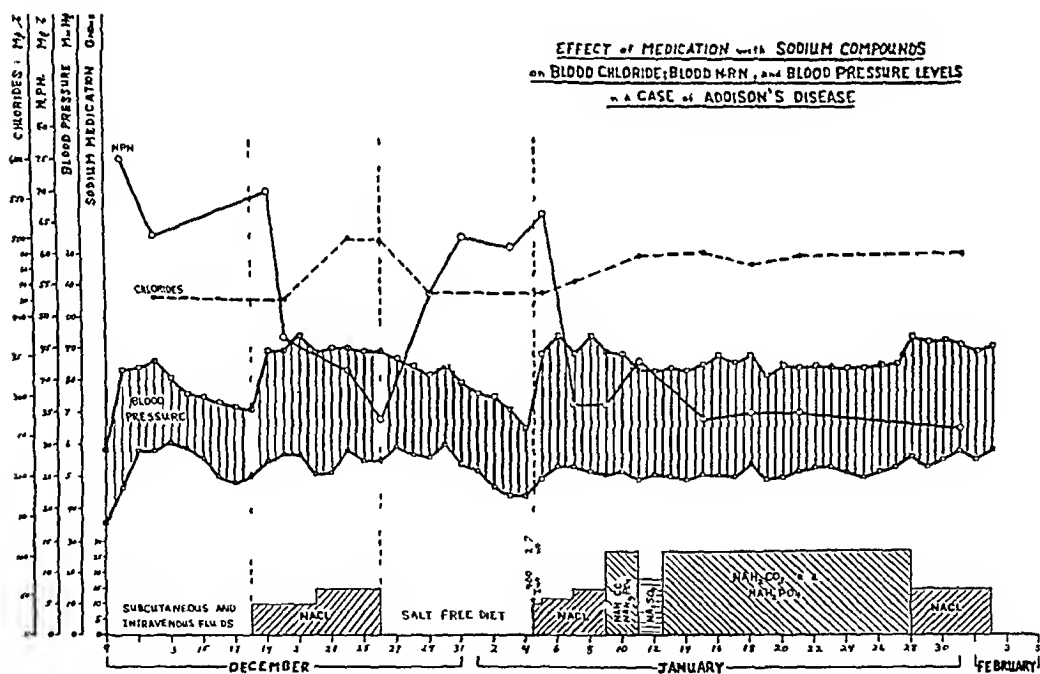


FIG 1 The typical low blood pressure and chloride levels and the elevated NPN in Addison's disease are relatively unaffected with fluids alone, but with sodium chloride are quickly restored to normal. The salt-poor diet confirms the diagnosis by reestablishing the original disease levels. Sodium medications other than the chloride prove equally efficacious in maintaining the values at normal levels. (The blood chloride and non-protein nitrogen levels were determined in every case after an overnight fast. The blood pressure values were calculated as an average of 9 to 12 readings over a period of 24 hours starting at 8 a.m. each day. All medications were given in 6 equal doses daily at 6, 9, 12, 3, 6, and 9 o'clock respectively. The sodium chloride was administered in 1 gram uncoated tablets, the sodium bicarbonate and sodium biphosphate were first given in tablet form, but the size of each dose made this unsatisfactory, later the bicarbonate was given as a powder followed by the biphosphate in solution with syrup of sarsaparilla, proving to be a convenient method of administration. The sodium sulphate was given in 2 gram capsules, but was discontinued because of the effect on the bowel. The subcutaneous and intravenous fluids consisted of physiological saline and 5 per cent glucose. The salt-poor diet consisted of the usual house diet with certain foods of high salt content exempted, served without a salt shaker. The chloride values are given as chloride in plasma.)

The following day further restriction of salt was attempted, and the patient soon exhibited marked dyspnea and restlessness, profound prostration, anorexia and vomiting. The blood pressure dropped to 65 systolic and 44 diastolic and the non-protein nitrogen returned to 66.

The effect of the salt-poor diet was thought sufficiently conclusive to terminate the test at this point. Four hundred c c of a 2 per cent sodium chloride solution were given intravenously with marked subjective improvement within several hours. The patient was then returned to 15 grams of sodium chloride daily by mouth, and in three days was again in good health.

It was decided to demonstrate the specificity of the sodium ion by substituting other sodium salts for the chloride. Sodium sulphate was used, but soon proved unsatisfactory because of the effect on the bowel. Sodium bicarbonate as a powder, and sodium biphosphate in solution with syrup of sarsaparilla were then given in quantity sufficient to supply sodium equal to that in 15 grams of sodium chloride. The patient continued to improve on this therapy for 18 days. The blood chemistry studies re-

TABLE I
Effect of Medication with Sodium Compounds on Blood Chloride, Blood Non-Protein Nitrogen, and Blood Pressure Levels in a Case of Addison's Disease

Date	N P N mg %	Chlorides* as Cl mg %	Average Blood Pressure mm of mercury		Medication
			Systolic	Diastolic	
12-9-34	—	—	58	36	Subcutaneous and intravenous fluids
10	75	—	83	47	
11	—	—	84	58	
12	63	335.1	86	58	
13	—	—	81	61	
14	—	—	76	59	
15	—	—	75	56	
16	—	—	73	50	
17	—	—	72	48	
18	—	—	71	50	10 grams NaCl daily by mouth
19	70	—	89	55	
20	46	332.9	89	57	15 grams NaCl daily by mouth
21	—	—	94	57	
22	—	—	88	51	
23	—	—	90	52	
24	41	366.6	90	58	
25	—	—	88	55	
26	34	366.6	88	55	Salt-poor diet started
27	—	—	86	59	
28	—	—	84	57	
29	54	337.2	82	56	
30	—	—	84	60	
31	63	—	79	54	
1-1-35	—	—	76	52	
2	—	—	75	47	
3	61	—	71	44	
4	—	—	65	44	400 c c 2% NaCl intrav, 12 grams NaCl daily by mouth
5	66	337.2	88	49	
6	—	—	94	53	15 grams NaCl daily by mouth
7	36	343.7	88	53	
8	—	—	94	52	

TABLE I (Continued)

Date	N P N mg %	Chlorides* as Cl mg %	Average Blood Pressure mm of Mercury		Medication
			Systolic	Diastolic	
9	36	—	89	51	9 gm NaH ₂ CO ₃ and 18 gm NaH ₂ PO ₄ daily by mouth 18 grams Na ₂ SO ₄ daily by mouth
10	—	—	88	52	
11	43	361 0	83	49	
12	—	—	83	51	9 gm NaH ₂ CO ₃ and 18 gm NaH ₂ PO ₄ daily by mouth
13	—	—	84	50	
14	—	—	83	49	
15	34	361 0	85	51	
16	—	—	88	51	
17	—	—	86	50	
18	35	358 1	88	54	
19	—	—	82	49	
20	—	—	85	50	
21	35	361 0	84	52	
22	—	—	85	53	
23	—	—	84	53	
24	—	—	84	52	
25	—	—	84	50	
26	—	—	85	52	
27	—	—	86	53	
28	—	—	95	57	15 grams NaCl daily by mouth
29	—	—	93	53	
30	—	—	93	56	
31	33	361 0	92	58	
2-1-35	—	—	90	56	
2	—	—	92	59	

* Plasma

vealed normal findings, and the blood pressure remained 85 systolic and 52 diastolic throughout the period. The serum protein, the albumin-globulin ratio, the carbon dioxide combining power of the blood, the glucose tolerance test, and the basal metabolic test were all within normal limits. The specificity of the sodium ion was apparent.

The patient was then returned to 15 grams of sodium chloride daily, and after another week of continued good health was discharged on a maintenance dosage of 12 grams a day. Because of the expense of supplying sodium chloride in tablet form, the municipal dispensary placed the patient on 12 grams by mouth in bulk. On this the patient soon developed oral and gastric distress, and lapsed into a state of restlessness and weakness. He was quickly restored to excellent health by substituting 1 gram tablets for the bulk salt. The patient has continued to take his medication daily and has remained well for nearly six months at this writing*. Figure 1 and table 1 show the effect of sodium medication on the blood chloride, blood non-protein nitrogen, and blood pressure levels in this case.

The 11 cases of Addison's disease treated with sodium compounds, which are summarized in the body of this article, represent the previously

* April 1936. Fourteen months after discharge our patient is in excellent health, with a blood pressure systolic 110, diastolic 74. He is faithfully taking 12 grams of sodium chloride each day.

published cases as determined by a search of the literature. The effect of sodium medication on the blood sodium level in nine of these is shown in figure 2 and in table 2.

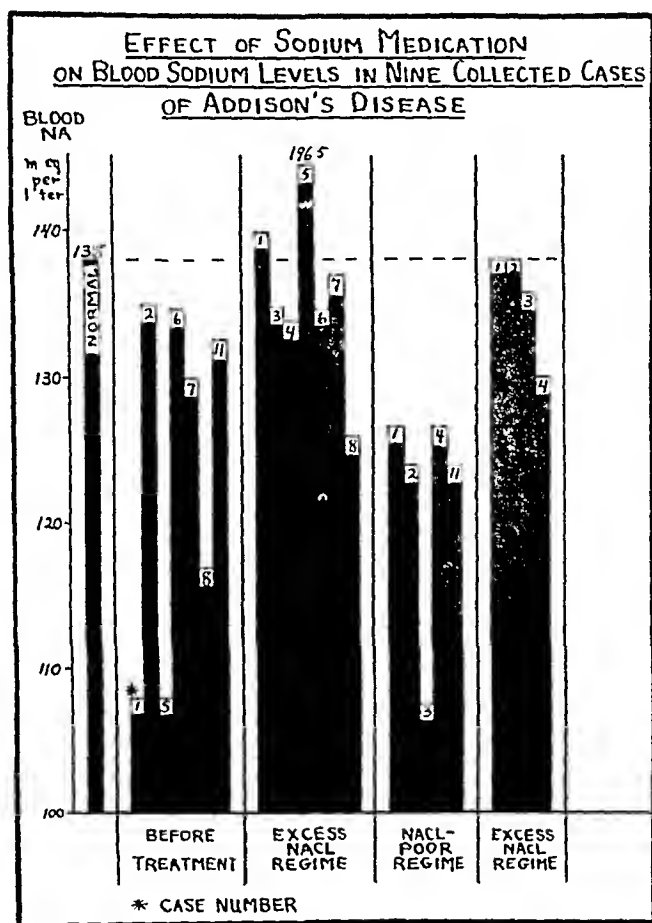


FIG 2 The blood sodium levels in nine cases of Addison's disease collected from the literature were below normal before any treatment with sodium compounds was instituted. On an excess salt regime there was a rise in the level in every instance except in case 6, where the value was unchanged. There was a fall in the level in all cases on a salt-poor regime, and a rise toward normal in all when excess salt was again given. (The blood sodium levels of the various authors have been converted to milli-equivalents per liter in order that this comparison could be made. The milligram per cent values are given with the case summaries. The sodium is expressed as sodium in plasma, not whole blood. The normal value of 138 milli-equivalents per liter is that given by Loeb¹⁸.)

CONCLUSIONS ON THE RELATION OF SODIUM TO ADRENAL DYSFUNCTION

1 The sodium level in the blood serum is found to be considerably decreased in bilaterally adrenalectomized animals.

2 In patients suffering from Addison's disease a similar decrease in the sodium level of the blood serum is present.

3 Sodium solutions will prolong the life of adrenalectomized animals, and when used with cortical extract, the amount of cortical preparation re-

TABLE II
Effect of Sodium Medication on Blood Sodium Levels in Nine Collected Cases of Addison's Disease

Case *	Author	Blood Sodium Levels in Milligrams Per Cent, Normal 138			
		Before Treatment	Excess NaCl Regime	NaCl- Poor Regime	Excess NaCl Regime
1	Loeb ^{18 19}	107.8	139.9	126.8	138.0
2	Loeb, et al ²⁰	135.0	—	124.0	138.0
3	Harrop, et al ²¹	—	134.8	106.6	135.8
4	Harrop, et al ²¹	—	133.9	126.8	130.0
5	Sears ²²	107.8	196.5	—	—
6	Snell ²³ , Wilder ²⁷	134.7	134.7	—	—
7	Howell ²⁴	130.0	137.0	—	—
8	Nettrour and Rynearson ²⁵	117.5	126.2	—	—
11	Loeb, et al ^{19b}	132.6	—	124.0	—

* Case numbers refer to the order of case summaries in this article

quired is much diminished. Sodium solutions alone will not prolong the life of adrenalectomized animals indefinitely, unless accessory glands are present and hypertrophy sufficiently to supply adequate cortical hormone. Sodium compounds therefore are not a substitute for cortical extract but an adjuvant.

4. Sodium administered to patients with Addison's disease will either render them symptomless, or else minimize the amount of cortical extract required to maintain them in relatively good health. In some cases sodium alone will bring about a complete remission of a severe relapse. Several patients treated with sodium salts alone still continue to remain well after more than a year, and the span of life of many other patients to date seems to have been indefinitely prolonged.

5. The loss of cortical hormone in Addison's disease apparently removes the normal regulatory mechanism of the blood sodium level, which consequently falls, initiating the train of symptoms known as adrenal insufficiency. An associated secondary deficiency in the hormone from the anterior lobe of the pituitary body has recently been suggested.

6. A confirmatory test for Addison's disease of considerable value is the salt-poor diet, which will provoke a typical crisis in a true case of adrenal insufficiency and thereby aid in establishing the diagnosis.

SUMMARY

1. The treatment of Addison's disease by the Munhead regime, and by cortical extract substitution therapy is briefly outlined.

2. The experimental and clinical evidence of the value of medication with sodium compounds in this disease is reviewed.

3. A case of Addison's disease which illustrates the beneficial thera-

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds
(One Original Case and 11 Collected from the Literature)

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels*						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me /lit normal	mg % normal	me /lit normal	mg % normal	me /lit normal	mg % normal	
1	Loeb 18	7 19 32 Admission	Progressive weakness, anorexia, loss of weight, increasing pigmentation of skin, nipples and buccal membranes, mild secondary anemia	90/60	123 5 138	284 317 4	88 6 103	314 5 365 6	5 3 4 8	20 7 18 7	Observation
		7 26 32 After 1 week of observation	Condition severe, profound exhaustion, slight dyspnea, increasing nausea, recurrent vomiting	65/48	107 8	247 9	72 7	258 0	7 1	27 7	NaCl 9 5 grams by proctoclysis and 5 grams in capsules daily, 10 c c escharin
		7-30 32 After 4 days on NaCl, discharged	Striking improvement	102/70	133 0	305 9	93 8	332 9	5 1	19 9	Liberal salt diet plus 1½ teaspoonfuls salt daily
		11 14 32 After 3 mo on NaCl	Gained 11 pounds, doing house work, no vomiting	112/74	139 9	321 7	107 3	380 9	4 6	17 9	Same treatment continued
		1 17 33 After 5 mo on NaCl	Vomited once after strenuous work, puffiness at night and edema under eyes in morning, urine normal	122/80	---	---	---	---	---	---	Placed on salt poor diet to relieve edema
		1 19 33 After 2 days on salt poor diet	Extreme prostration, forced to go to bed	---	---	---	---	---	---	---	Salt poor diet continued
		1 24 33 After 7 days on salt poor diet, readmitted	Continuous vomiting, progressive weakness, loss of 7 pounds weight	86/60	126 8	291 6	92 3	327 6	5 7	22 2	7 grams NaCl orally daily Proctoclysis 200 c c physiological saline every 4 hours
		1 27 33 After 3 days on NaCl	Much improved	---	---	---	---	---	---	---	Rectal taps stopped Oral salt continued
		1 30 33 After 6 days on NaCl discharged	Feeling very well, gained 4 pounds	122/80	138 0	317 4	103 5	367 4	5 0	19 5	Oral salt continued

* The blood serum electrolyte readings of the various authors have been expressed in terms of mille-equivalents per liter and in milligrams per 100 c c in order that comparisons can be made. The mille-equivalent values given by Loeb 18 are used as average normal readings. The sodium has been expressed as sodium, the chloride as chloride, and the potassium as potassium in every case. All values are plasma readings, not whole blood.

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

1	Loeb ¹⁹	4-10 33 After 3 mo on NaCl	Feeling well	—	138 0	317 4	104 4	370 6	4 8	18 7	Increased to 15 grams NaCl daily on own initiative
		11-9 33 After 10 mo on NaCl	18 months after first admission improvement maintained complaints only of feeling cold and tired rather easily pigmentation slightly decreased	normal	138 0	317 4	104 2	369 9	4 8	18 7	15 grams NaCl daily continued
		10 13 34 After 21 mo on NaCl	More than 2 years after first admission still relatively well	—	—	—	—	—	—	—	NaCl continued
2	Loeb et al. ²⁰	Before admission	Past history of tuberculous hip and pleurisy with effusion Irregular abdominal pain and occasional vomiting for 2 years Increasing brown pigmentation for 1 year Weakness and dyspnea with slight cough for 6 months	112/80 to 76/50	—	—	—	—	—	—	None
		Admission, placed on normal diet	Up and about the ward for 18 days with nausea occasional abdominal pain slowly increasing weakness	—	135	310 5	—	—	—	—	Salt-poor diet
		After 2 days on salt-poor diet	Much worse with dizziness nausea increased prostration Vomited 200 cc in 48 hours	—	124	285 2	—	—	—	—	20 grams NaCl orally daily
3	Harrop et al. ²¹	After 2 days on NaCl	Improved remarkably out of bed	—	—	—	—	—	—	—	Oral salt continued
		After 5 days on NaCl, discharged	Much improved	—	138	317 4	—	—	—	—	Maintenance dosage 10 grams NaCl daily with highly salted diet
		Admission	Known case of Addison's disease with roentgen ray evidence of calcification	—	—	—	—	—	—	—	High salt diet and low potency cortical extract
		After 9 months on high salt diet and low potency extract	Patient symptomless gaining weight and strength	—	—	—	—	—	—	—	High salt diet and sterile hypo in stead of extract
		After 6 weeks on high salt diet and sterile hypo	Relapse	—	—	—	—	—	—	—	High salt diet and low potency cortical extract resumed
		After several days on high salt diet and low potency extract	Improved	—	134 8	300 0	106 8	379 1	—	—	Low salt diet and low potency cortical extract
		After 4 days on salt-poor diet and low potency extract	Marked weakness and anorexia, severe relapse	—	106 6	215 1	81 2	288 2	—	—	Low salt diet discontinued Intravenous saline begun cortical extract continued

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels *						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me./lit. normal	mg % normal	me./lit. normal	mg % normal	me./lit. normal	mg % normal	
3	Harrop et al. (Cont.)	After 9 days on salt and low potency ex- tract	Much improved	—	128.2	294.8	96.8	313.6	—	—	High salt diet and cortical extract
		After 18 days on salt and low potency ex- tract	Apparently normal	—	135.8	302.3	102.4	363.5	—	—	High salt diet and cortical extract
4	Harrop et al.	Admission	Known case of Addison's disease, feeling very well on high salt diet and low potency cortical extract	—	133.9	307.9	103.6	367.7	—	—	High salt diet and cortical extract discontinued. Phased on salt poor diet
		After 5 days on salt poor diet without ex- tract	Severe relapse	—	126.8	291.6	95.2	337.9	—	—	11 grams NaCl daily
		After 6 days on salt only	Much improved	—	130.0	299.0	100.0	355.0	—	—	11 grams NaCl daily
5	Serra	1927	Diagnosed Addison's disease	—	—	—	—	—	—	—	None
		1931	Mild relapse	—	—	—	—	—	—	—	Course of cortical extract injec- tions
		1932	Increasing weakness, anorexia, vomiting, giddiness, precordial pain	125/88	—	—	—	—	—	—	More extract given
		3-10-34 Admission	Recurrence 4 weeks before, with increasing weakness, giddiness, slight cough and increasing pig- mentation of axillae, nipples, back of neck, buccal membrane and palate	120/80	107.8	248	75.5	268	11.3	56	Regular diet with 5 grams of NaCl daily
6	Snell ³	3-17-34 After 1 week on regular diet with 5 grams NaCl daily Discharged	Generally improved, weakness gone, able to get about without difficulty	140/85	196.5	452	128.1	155	11	16	Advised to continue NaCl
		1911 to 1923	Bilateral pulmonary tuberculosis in early life 1917 diffuse pig- mentation of skin 1922 weak- ness 1923 severe continuous lumbar pain	—	—	—	—	—	—	—	None

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

6	Snell (Cont.)	1923 to 1929	Extreme weakness, increased pigmentation, palpable cervical glands, rales in both apices, roentgen ray of lungs positive on admission in 1923. Improved sufficiently on Muirhead regime to go home in 2 weeks where it was continued. 1924 tuberculous adenitis proved at biopsy. Iodine treatment. 1929 in good health. Muirhead treatment stopped.	110/80 100/75	—	—	—	—	—	—	Muirhead treatment epinephrine orally, rectally and subcutaneously at frequent intervals up to patient's tolerance daily with desiccated cortex orally 10 to 15 grams daily
Wilder 7		1929 to 1934	1932 failing strength increasing fatigue marked craving for salty food. March 1934 losing weight.	—	—	—	—	—	—	—	None
		5 16 34 Admission	Marked weakness confusion loss of memory severe constipation pigmentation of exposed surfaces oral mucosa and genitalia, weak faint heart both adrenals calcified on roentgen ray	110/65	134 7	310 0	92 9	330 0	4 9	19 3	Intramuscular cortical extract (Kendall) sodium chloride 10 grams orally, and 1 liter physiologic saline daily
		After several days discharged	Much improved in 24 hours, followed by gain in weight, increased appetite and strength	—	134 7	310 0	105 8	375 6	4 9	19 3	10 grams NaCl daily recommended on discharge
		July 1934 after 2 months on 10 grams NaCl daily	Well for 2 months. Admitted again in mild crisis improved with treatment, discharged	—	—	—	—	—	—	—	6 cc cortin, 8 grams of salt pills and salt diet daily
		9 30 34 Admission after 2 months on 6 cc cortin and 8 grams NaCl daily plus salt diet	Severe crisis with abdominal pain nausea vomiting restlessness hic cough and extreme weakness	—	—	—	—	—	—	—	Cortin and 0.9% NaCl by vein for 2 days then 6 mg cortin and 8 grams NaCl in pills plus 6 grams in diet daily
		10 4 34 After cortin and NaCl intravenously and orally	Out of bed but still weak and rest less	—	—	—	—	—	—	—	0.3 cc anterior pituitary extract daily in addition
		10 9 34 After 5 days on cortin NaCl and anterior pituitary	Marked improvement stronger than in many months	—	—	—	—	—	—	—	Salt pills omitted receiving only 6 grams NaCl in diet cortin and anterior pituitary extract continued
		10 11 34 After 4 days on cortin and anterior pituitary only	Weaker with nausea and hicough	—	—	—	—	—	—	—	NaCl by vein, daily salt pills resumed, cortin continued, anterior pituitary extract stopped
		10 23 34 After 8 days on cortin and NaCl	Improved, some residual weakness	—	—	—	—	—	—	—	Salt again restricted to diet, cortin continued

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels *						Treatment Prescribed	
					Sodium		Chloride		Potassium			
					me./lit. normal 138	mg. % normal 317.4	me./lit. normal 103	mg. % normal 365.6	me./lit. normal 4.8	mg. % normal 18.7		
6	Wilder (Cont.)	10-25 34 After 2 days on cortin and limited NaCl	Marked weakness with hiccough and nausea	—	—	—	—	—	—	—	Intravenous NaCl given, daily salt pills resumed, cortin continued	
		10 27 34 After 2 days on cortin and full NaCl as before	Symptom free	—	—	—	—	—	—	—	Cortin discontinued, NaCl as before and 0.3 cc anterior pituitary extract given daily	
		11 2 34 After 6 days on NaCl and anterior pituitary extract, no cortin	Fading rapidly	—	—	—	—	—	—	—	Cortin resumed with daily NaCl and anterior pituitary extract	
		11 9 34 After 7 days on NaCl cortin and anterior pituitary extract	In good health	—	—	—	—	—	—	—	Same treatment continued	
		1933 Before admission	August 1933 pigmentation of skin November 1933 weakness, lassitude, anorexia, dyspnea on slight exertion, swelling of ankles	—	—	—	—	—	—	—	None	
7	Howell †	2 11 34 Admission	Extreme exhaustion, nausea, vomiting, loss of 56 pounds weight, characteristic pigmentation on buccal membranes, weak heart and pulse mild secondary anemia	60/40 78/48	130.0	298.0	—	—	—	—	Observation	
		2 23 31 After 1 week of observation	Condition unchanged + nausea listless apathetic	—	—	—	—	—	—	—	—	10 grams NaCl daily
		2 24 34 After 24 hours on 10 grams NaCl daily	Dramatic effect sitting, up reading, appetite improved, nausea gone	—	—	—	—	—	—	—	—	10 grams NaCl daily continued
		3 9 34 After 14 days on 10 grams NaCl daily	Patient allowed up as well in months	—	130.8	301.0	—	—	—	—	—	Salt continued
		3-15 34 After 19 days on 10 grams NaCl daily	Patient in good health	—	—	—	—	—	—	—	—	NaCl reduced to 5 grams daily without patient's knowledge

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

7	Howell (Cont.)	3-19-34 After 4 days on 5 grams NaCl daily	No subjective changes noted	—	137 0	315 0	—	—	—	5 grams NaCl daily continued
		3-26-34 After 11 days on 5 grams NaCl daily	Weakness, loss of appetite, vom- ited several times	—	—	—	—	—	—	Returned to 10 grams NaCl daily
		4-5-34 After 10 days on 10 grams NaCl daily Discharged	Marked improvement	75/45	—	—	—	—	—	To continue NaCl
8	Netttrour and Kyncar son ²⁵	1932 to 1934 Before admission	1932 progressive fatigue, too tired to study, failed in college Feb and Apr 1934 acute upset with slight cough, nausea, vomit- ing, slight questionable jaundice, extreme weakness, loss of 18 pounds weight	—	—	—	—	—	—	None
		8-4-34 Admission	Thin tired male no definite pig- mentation, mild anemia, adrenals not calcified, chest roentgen ray negative, B M R -27 and -22	78/52 106/68	117 5	271 4	95 9	340 4	20 2	Placed on salt-poor diet to aid in diagnosis
		8-9-34 After 5 days on salt poor diet	Nausea, vomiting, and extreme weakness	86/50	—	—	83 2	295 5	—	Intravenous saline 10 c c cortical extract daily first 2 days, 8 gm NaCl daily by mouth
		8-13-34 After 4 days on NaCl and cortical extract	Patient improved no weakness headache epigastric distress nau- sea or vomiting	—	126 2	290 4	89 7	350 7	—	8 grams NaCl daily continued
9	Wilder ²⁷	1913 to 1934	1913 acute tuberculous salpin- gitis and peritonitis 1929 found to be essentially well Fall 1933 fatigue anorexia loss of weight black freckles and pigmentation of gums	—	—	—	—	—	—	None
		February 1934	Diagnosed Addison's disease	—	—	—	—	—	—	Salt pills 8 grams daily
		9-27-34 After 7 mo on salt, admission	Condition unchanged	—	—	—	—	—	—	Salt poor diet to confirm diagnosis
		9-29-34 After 2 days on salt-poor diet	Nausea, lightheadedness, sudden collapse with severe abdominal pain and cyanosis	—	—	—	—	—	—	20 grams NaCl and 20 milligrams of cortin by vein
		9-30-34 After cortin and NaCl by vein	Much improved in 24 hours	—	—	—	—	—	—	10 mg. cortin daily, salt restricted to diet (6 grams)
		10-2-34 After 3 days on cortin and limited NaCl	Prostrated, acutely ill	—	—	—	—	—	—	Cortin 6 mg, anterior pituitary extract 0.3 c c, total NaCl 14 grams daily

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels *						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me /lit normal 138	mg % normal 317.4	me /lit normal 103	mg % normal 365.6	me /lit normal 4.8	mg % normal 18.7	
9	Wilder (Cont.)	10 9 34 After 7 days on cortin, NaCl and anterior pituitary extract	Marked improvement symptom free, with increased endurance gain in weight	—	—	—	—	—	—	—	Cortin and anterior pituitary continued, salt restricted to diet (6 grams)
		10 17-34 After 8 days on anterior pituitary, and cortin, NaCl restricted	Weakness, restlessness, and nausea	—	—	—	—	—	—	—	Salt by mouth and vein, cortin continued, anterior pituitary extract discontinued
		10 22 34 After 5 days on cortin and NaCl	In good health	—	—	—	—	—	—	—	Salt restricted, 6 mg cortin continued
		10 24 34 After 2 days on cortin only	Extreme weakness, nausea and hiccough	—	—	—	—	—	—	—	Salt cortin and anterior pituitary resumed daily
		10 30 34 After 6 days on cortin, NaCl and anterior pituitary extract	In good condition	—	—	—	—	—	—	—	Cortin stopped, anterior pituitary and NaCl continued
		11-3 31 After 4 days on anterior pituitary and NaCl no cortin	Weakness, nausea, restlessness, loss of weight	—	—	—	—	—	—	—	Cortin resumed, anterior pituitary and NaCl continued
10	Blankenhorn and Hayman ²³	9 9 33 Admission	Pigmentation of skin, palate gums and buccal membrane. Vomiting, weakness, loss of weight for 3 months, roentgen ray calcification over upper pole of left kidney. Diagnosed Addison's disease	108/55	—	87.3	310.0	—	—	—	Full diet and salt ad lib
		9 12 33 After 3 days on full diet and salt ad lib	Severe crisis, repeated vomiting, irrational	80/40	—	—	—	—	—	—	750 cc physiologic saline intravenously
		9 13 33 After 1 day on normal saline by vein	Temporary improvement followed by vomiting with patient still irrational	—	—	76.1	270.0	—	—	—	2250 cc saline subcutaneously and intravenously
		9-14-33 After 2 days on normal saline by vein and under skin	Marked improvement	—	—	—	—	—	—	—	12 grams NaCl daily in capsules

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

10	Blankenhorn and Hayman (Cont.)	Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued									
		10 1 33 After 17 days on NaCl	Continued improvement	110/75	—	—	94.3	335.0	—	—	12 grams NaCl daily continued
		10 3 33 After 19 days on NaCl	In good condition	—	—	—	—	—	—	—	Placed on salt-poor diet to confirm diagnosis
		10 5 33 After 2 days on salt poor diet	Despondent irritable, voluntarily remained in bed	110/75	—	—	—	—	—	—	Salt-poor diet continued
		10 8 33 After 5 days on salt poor diet	Mental condition worse nauseated	105/80	—	—	89.3	317.0	—	—	Salt poor diet continued
		10 11-33 After 8 days on salt poor diet	Condition grave	85/55	—	—	82.2	292.0	—	—	30 cc cortical extract with salted food next day same with 30 cc intramuscularly
		10 13 33 After 2 days of cortical extract treatment	No improvement	—	—	—	74.9	266.0	—	—	Glucose and saline intravenously
		10 14 33 After 1 day on glucose and saline by vein	Definite improvement in 12 hours marked in 36 hours	—	—	—	78.9	280.0	—	—	12 grams NaCl daily in capsules resumed
		10 16 33 After 3 days on NaCl	Out of danger	—	—	—	92.1	327.0	—	—	NaCl continued
		10 23-33 After 10 days on NaCl	In good health pigmentation faded	105/75	—	—	—	—	—	—	NaCl continued
		11 5 33 After 22 days on NaCl	In excellent condition	—	—	—	—	—	—	—	NaCl stopped Mixture of NH_4Cl and K chlorides substituted
		11 8 33 After 3 days on NH_4Cl , Ca, and KCl mixture	Abdominal pain nausea and vomiting	90/50	—	—	—	—	—	—	Intravenous saline then 12 grams NaCl daily
		11-9 33 After 1 day on NaCl	Immediate improvement	—	—	—	—	—	—	—	NaCl continued
		11-23 33 After 14 days on NaCl	In good condition	—	—	—	—	—	—	—	NaCl stopped Mixture of sodium sulphate sodium bicarbonate and sodium biphosphate substituted
		12 10 33 After 17 days on sodium salts other than chloride Discharged	No discomfort Patient continued to feel very well	—	—	—	—	—	—	—	Placed on full diet with 16 grams NaCl daily in capsules

Summaries of 12 Cases of Addison's Disease Treated with Sodium Compounds—Continued

Case	Author	Observation Interval	Clinical Findings	Blood Pressure	Blood Serum Electrolyte Levels*						Treatment Prescribed
					Sodium		Chloride		Potassium		
					me./lit. normal 138	mg. % normal 317.1	me./lit. normal 103	mg. % normal 365.6	me./lit. normal 4.8	mg. % normal 18.7	
10	Blankenhorn and Hayman (Cont.)	12 20 33 After 10 days on NaCl 1 4 34 After 25 days on NaCl	Feeling strong, good appetite Appetite poor, sleepless, irritable, confused, profound crisis. Developed bronchopneumonia and died no postmortem	120/80 —	— —	— 122.2	— 134.0	— —	— —	16 grams NaCl continued Saline and glucose intravenously, 20 cc cortical extract intravenously	
11	Loeb et al. ¹⁰	Admission After 5 days on salt poor diet After 24 hours of infusion treatment After 7 days of infusion treatment	Classical signs and symptoms of Addison's disease for 8 months. Severe anorexia and weakness present 2 weeks Increasing weakness, drowsiness and anorexia for 4 days, sudden crisis semi comatose imperceptible pulse blood sugar 48 ketosis present No change in condition shock persisting. Blood sugar normal ketosis absent General health greatly improved vomiting stopped, strength and appetite returning	82/60 58/50 62/40 —	132.6 129.4 124.0 —	304.9 297.6 285.2 —	— — — —	— — — —	— — — —	Salt-poor diet 25 cc cortical extract intravenously, frequent epinephrine injections, continuous infusion salt solution and dextrose Continuous infusion of salt solution and dextrose continued Regular diet with 10 grams NaCl daily	
12	Reifenstein and Reifenstein	1932 to 1934 12 9 34 Admission	May 1932 nausea vomiting chills fever and extreme weakness. Fall 1932 bronze pigmentation of skin. June-July 1934 in bed with extreme weakness. August 1934 increasing fatigue. Dec 8 1934 acute diarrhea vomiting prostration Acutely ill in state of collapse nausea vomiting chills, dyspnea excessive perspiration, diarrhea, and generalized weakness. Pig	— 58/36	— —	— 94.4	— 335.1	— —	— —	None Glucose and normal saline subcutaneously and intravenously	

peutic effect of sodium medication, the value of the confirmatory salt-poor diet test, and the specificity of the sodium ion in treating this disease is presented

4 Eleven other cases treated with sodium collected from the literature are summarized

REFERENCES

- 1 MUIRHEAD, A L Autograph history of case of Addison's disease, Jr Am Med Assoc, 1921, lxxvi, 652
- 2 SWINGLE, W W, and PFIFFNER, J J The revival of comatose adrenalectomized cats with an extract of the suprarenal cortex, Science, 1930, lxxii, 75
- 3 HARTMAN, F A, and BROWNELL, K A The hormone of the adrenal cortex, Science, 1930, lxxii, 76
- 4 SNELL, A M Diagnosis and treatment of Addison's disease with reference to series of 46 patients treated with suprarenal cortical hormone, Internat Clin, 1934, iii, 46-62
- 5 STEWART, G N Adrenalectomy and relation of adrenal bodies to metabolism, Physiol Rev, 1924, iv, 163-190
- 6 STEWART, G N, and ROGOFF, J M Studies on adrenal insufficiency, Proc Soc Exper Biol and Med, 1925, xxii, 394-397
- 7 BANTING, F G, and GAIRNS, S Suprarenal insufficiency, Am Jr Physiol, 1926, lxxvii, 100-113
- 8 LUCAS, G H W Blood and urine findings in desuprarenalized dogs, Am Jr Physiol, 1926, lxxvii, 114-125
- 9 COREY, E L Effect of forcing fluids upon survival after bilateral epinephrectomy, Am Jr Physiol, 1927, lxxix, 633-640
- 10 ZWEMER, R L Experimental study of adrenal cortex II Prolongation of life after complete epinephrectomy, Am Jr Physiol, 1927, lxxix, 658-665
- 11 BAUMANN, E J, and KURLAND, S Changes in inorganic constituents of blood in suprarenalectomized cats and rabbits, Jr Biol Chem, 1927, lxxi, 281-302
- 12 MARINE, D, and BAUMANN, E J Duration of life after suprarenalectomy in cats, and attempts to prolong it by injections of solutions containing sodium salts, glucose, and glycerol, Am Jr Physiol, 1927, lxxxi, 86-100
- 13 LOEB, R F Chemical changes in blood in Addison's disease, Science, 1932, lxxvi, 420-421
- 14 BUTLER, A M, and TUTHILL, E An application of the uranyl zinc acetate method for determination of sodium in biological material, Jr Biol Chem, 1931, xciii, 171-180
- 15 ATCHLEY, D W, and BENEDICT, E M Serum electrolyte studies in normal and pathological conditions pneumonia, renal edema, cardiac edema, uremic and diabetic acidosis, Jr Clin Invest, 1930, ix, 265-294
- 16 LOEB, R F, ATCHLEY, D W, BENEDICT, E M, and LELAND, J Electrolyte balance studies in adrenalectomized dogs with particular reference to excretion of sodium, Jr Exper Med, 1933, lvii, 775-792
- 17 HARROP, G A, SOFFER, L J, ELLSWORTH, R, and TRESCHER, J H Studies on suprarenal cortex III Plasma electrolytes and electrolyte excretion during suprarenal insufficiency in dog, Jr Exper Med, 1933, lviii, 17-38
- 18 LOEB, R F Effect of sodium chloride in treatment of patient with Addison's disease, Proc Soc Exper Biol and Med, 1933, xxx, 808-812
- 19 a LOEB, R F, and ATCHLEY, D W Significance of salt in treatment of Addison's disease, Med Clin N Am, 1934, xvii, 1317-1323
- b LOEB, R F, ATCHLEY, D W, and STAHL, J Role of sodium in adrenal insufficiency, Jr Am Med Assoc, 1935, civ, 2149-2154

- 20 LOEB, R F, ATCHLEY, D W, GUTMAN, E B, and JILLSON, R On mechanism of sodium depletion in Addison's disease, *Proc Soc Exper Biol and Med*, 1933, xxxi, 130-133
- 21 HARROP, G A, WEINSTEIN, A, SOFFER, L J, and TRESCHER, J H Diagnosis and treatment of Addison's disease, *Jr Am Med Assoc*, 1933, c, 1850-1855
- 22 SFARS, W G Case of Addison's disease treated with common salt, *Lancet*, 1934, i, 950-951
- 23 SNELL, A M Addison's disease of unusually long duration, *Proc Staff Meet Mayo Clin*, 1934, ix, 303-307
- 24 HOWELL, C M H Effects of common salt in Addison's disease, *Lancet*, 1934, i, 1116-1117
- 25 NETTROUR, W S, and RYNEARSON, E H Salt-poor diet as provocative test for Addison's disease, *Proc Staff Meet Mayo Clin*, 1934, ix, 550-556
- 26 TOUW, J F, and NOORDHOEK HEGT, W F Treatment of Addison's disease with sodium chloride, *Nederl Tijdschr v Geneesk*, 1934, lxxviii, 4439-4446
- 27 WILDER, R M Use of anterior lobe pituitary extract in treatment of Addison's disease, *Proc Staff Meet Mayo Clin*, 1934, ix, 689-693
- 28 CROOKE, A C, and RUSSELL, D S Pituitary gland in Addison's disease, *Jr Path and Bact*, 1935, xl, 255-283
- 29 GAMBLE, J L, ROSS, G S, and TISDALL, F F Metabolism of fixed base during fasting, *Jr Biol Chem*, 1923, lvi, 633-695
- 30 ATCHLEY, D W, LOEB, R F, RICHARDS, D W, JR, BENEDICT, E M, and DRISCOLL, M E On diabetic acidosis, a detailed study of electrolyte balances following the withdrawal and reestablishment of insulin therapy, *Jr Clin Invest*, 1933, xii, 297-326
- 31 FØLLING, A On mechanism of ammonium chloride acidosis, *Acta med Skandinav*, 1929, lxxi, 221-279
- 32 ZWEMER, R L Adrenal cortex and electrolyte metabolism, *Endocrinology*, 1934, xxviii, 161-169
- 33 BLANKENHORN, M A, and HAYMAN, J M Note on use of suprarenal extract and sodium salts in case of Addison's disease, *Am Jr Med Sci*, 1935, clxxxix, 419-423
- 34 RUBIN, M I, and KRICK, E T Effect of adrenalectomy on salt metabolism in rats, *Proc Soc Exper Biol and Med*, 1933, xxxi, 228-229
- 35 GAUNT, R, TOBIN, C E, and GAUNT, J H Effect of high salt diet on survival of adrenalectomized rats, *Proc Soc Exper Biol and Med*, 1934, xxxii, 134-136
- 36 SWINGLE, W W, PEIFFNER, J J, VARS, H M, and PARKINS, W M The effect of sodium chloride administration upon adrenalectomized dogs not receiving extract, *Am Jr Physiol*, 1934, cxviii, 159-167
- 37 Editorial Common salt for Addison's disease, *Lancet*, 1934, i, 137

THE LEUKOCYTE PICTURE IN HODGKIN'S DISEASE *

By GRACE M. ROTH, B S , and CHARLES H. WATKINS, M D , F A C P ,
Rochester, Minnesota

ALTHOUGH Hodgkin's ¹ disease was described by him as early as 1832, the blood picture in this disease was not seriously considered until 1910. At that time Fabian,² after a critical survey of the literature, reported that the blood picture was not sufficiently constant to be of any diagnostic value. He did state, however, that the most frequent hematologic finding in Hodgkin's disease was a moderate increase in the number of polymorphonuclear neutrophils and a relative decrease in the number of lymphocytes.

In 1911, following this survey, Bunting³ reported the analysis of a small series of blood counts in cases of Hodgkin's disease and described a specific blood picture for the diagnosis of the disease. He divided his cases into two distinct groups according to the differential count. In the first group, in which the disease had been present for less than a year, there was a normal or decreased percentage of polymorphonuclear neutrophils, in the second group, in which the disease had been present for more than a year, there was marked leukocytosis with an increase in the number of polymorphonuclear cells from 72 to 90 per cent. The transitional cells or monocytes were increased in both groups, the lymphocytes were sometimes increased in the early cases but showed a steady decrease as the disease progressed. Bunting also maintained that on examination of the blood smear a definite increase in the number of platelets was found.

In 1914 Bunting⁴ and Yates⁵ reported an additional group of cases of Hodgkin's disease with the same hematologic findings. In the period from 1915 to 1920 these findings of Bunting's were generally confirmed in isolated reports of cases. Also reported in this period were rare cases in which eosinophilia was present. The relationship between leukemia, sarcoma, and Hodgkin's disease received considerable attention at this time. Although the blood smear was used for differential diagnosis in some instances, the pathologic changes observed in excised lymph nodes were the criteria for differential diagnosis.

In 1920, however, Longcope and McAlpin⁶ in a comprehensive study of Hodgkin's disease stated that changes existed in the blood, which were so characteristic that they could be used to differentiate this disease from all other types of enlargement of lymph nodes. These constant changes consisted of a relative or absolute increase in the number of transitional cells (monocytes) and a total increase in the number of platelets throughout the

* Abstract of paper read before the Central Society for Clinical Research, Chicago, Illinois, November 1, 1935.

From the Mayo Foundation and the Division of Medicine, the Mayo Clinic, Rochester, Minn.

course of the disease. Relative or absolute eosinophilia seemed to be most marked when there was necrosis of the lymph nodes.

Following this survey with Longcope, in 1923 McAlpin⁷ studied 18 cases of Hodgkin's disease and arrived at conclusions somewhat contradictory to those of the earlier report. He stated that it would not be possible to diagnose Hodgkin's disease from examination of the blood smear. In this series of 18 cases the number of transitional cells was high in only eight cases and the platelets only in seven. When the cases were arranged in the order of their total leukocyte count there was no apparent relationship between this and the duration of the disease. The highest leukocyte count was 13,000 per cubic millimeter.

Weiss⁸ in 1924 reversed the original idea of an increase in polymorphonuclear neutrophils as being the most important finding and considered it to be instead the decrease in the number of lymphocytes. He stated that the neutrophils and eosinophils might be increased in number, and further suggested that a leukocytosis exceeding 20,000 cells per cubic millimeter warranted the suspicion that the diagnosis of Hodgkin's disease was incorrect.

The largest and most completely studied group of cases of Hodgkin's disease up to 1930 was reported by Falconer⁹. He had observed 40 cases, which he divided into two groups as Bunting had done. Falconer concluded that in the first group, in which the disease was of less than a year's duration, the total leukocyte and differential counts were within normal limits, whereas in the second group, in which the disease was of more than a year's duration, only a slight increase in the total leukocyte count occurred, with a slight increase in the percentage of polymorphonuclear cells at the expense of a decrease in the number of lymphocytes. Although Falconer had used Bunting's grouping of cases, his observations did not quite agree with the latter's. Falconer found, however, an average and fairly constant increase in the number of mononuclear cells. The eosinophile count averaged about normal or slightly below normal, although in one instance the percentage was very high. The platelet counts in Falconer's cases were not high.

Straube,¹⁰ in 1931, summarized his findings in 21 cases of Hodgkin's disease. He decided that no uniform or diagnostic hematologic picture for Hodgkin's disease existed, and that it was therefore not possible to establish the diagnosis on the basis of hematologic examination alone.

Thus the views regarding the diagnostic value of the blood picture in this disease differ greatly. Some workers consider the blood picture to be characteristic of the disease, whereas others are of the opinion that no characteristic blood picture exists. If there is a characteristic blood picture, it must have to do with the differential leukocyte count, as most investigators have found that in regard to the erythrocytes in general, a slight secondary anemia exists which is not in itself characteristic.

The present study was therefore undertaken to determine the diagnostic value of the blood picture in Hodgkin's disease. Owing to the fact that the method of determining blood platelets was changed during the course of this study, the platelets were not considered.

PLAN OF STUDY

The differential counts were made from blood smears in cases in which a diagnosis of Hodgkin's disease or lymphosarcoma was confirmed by pathologic study of an excised lymph node. The criteria for the diagnosis of lymphosarcoma were loss of normal architecture of the lymph node, absence of lymph follicles, and marked hyperplasia of the cellular elements, and for Hodgkin's disease fibrosis, with an increase of connective tissue throughout the node, presence of Dorothy Reed cells, and an increase in the number of eosinophiles in the node²¹. None of the patients had had any previous treatment. The duration of the disease was noted, and the cases were divided into four groups depending on the state of the disease when the patient was admitted to the clinic. Group I included those cases in which the disease was of six months' duration or less, group II included those cases in which the disease was of more than six but not more than 12 months' duration, group III included those cases in which the disease was of more than a year's but not more than two years' duration, and group IV included those cases in which the disease was of more than two years' duration. The longest duration was 13 years. The cases were also divided into four groups according to the situation and extent of the disease. Group A in which a single cervical, supraclavicular, or axillary lymph node was involved, group B in which a single inguinal lymph node was involved, group C in which two cervical, axillary, or supraclavicular lymph nodes were involved or in which a single lymph node in two of these situations was involved, and group D in which there was general adenopathy.

DATA

Sixty-five differential counts were made from blood smears in 40 cases of Hodgkin's disease and 18 differential counts were made from blood smears in nine cases of lymphosarcoma.

Group I In 12 of 25 differential counts, or 48 per cent, the percentage of neutrophils was greater than 68, the highest being 85. The shift to the left was not marked, the nonfilament count of the polymorphonuclear neutrophils being only 8.1 cells in 200. The average percentage of lymphocytes was well within the normal limits of 25 to 30. In 15 of 25 counts, or 60 per cent, the percentage of lymphocytes was less than 25, in 20 per cent of the counts it was greater than 30. The average percentage of monocytes was within normal limits, in five counts, or 20 per cent, it was greater than eight. The average percentages of eosinophiles and basophiles were within normal limits, in one instance being 8.5.

Group II In this group, in which the disease had existed from six months to one year, four of the 11 patients, or 36 per cent, had leukocyte counts higher than 8000, whereas two had counts lower than 5000 per cubic millimeter. The average percentage of polymorphonuclear neutrophils was slightly higher than in group I but was at the upper limit of normal, in nine of 17 counts the percentage was greater than 70, whereas in two it was less than 60. The nonfilament count showed only a very slight increase over that in group I. The average percentage of lymphocytes was definitely decreased below normal, in 14 of 17 counts being less than 25. The average percentage of monocytes was slightly increased, in seven of 17 counts, or 41 per cent, being more than eight. The percentages of eosinophiles were all within normal limits.

Group III Seven of the nine patients in this group, or 77.8 per cent, had leukocyte counts greater than 8000 per cubic millimeter. The greatest increase in the percentage of polymorphonuclear neutrophils took place in this group. In 12 of 16 counts, or 75 per cent, this percentage was increased above 68. The shift to the left was almost doubled in this as compared to groups I, II, and IV. The average percentage of lymphocytes, on the other hand, was the lowest of any of these groups, of 16 counts on the nine patients in the group, 15, or 94 per cent, were below 25. In 16 counts of monocytes, or 25 per cent, the percentages were more than eight. The percentage of eosinophiles was 1.8, in all but two instances being within normal limits. The basophiles likewise were within normal limits.

Group IV The leukocyte count in this group was the lowest of any of these groups. The average percentage of polymorphonuclear neutrophils in this group could hardly be called abnormal, in four of the eight counts the percentage was above 68. The shift to the left or nonfilament count was slightly increased over the previous groups. The average percentage of monocytes was seven, with only two counts being above the normal eight. The average eosinophile count was the highest of any of the groups, although only two counts were above the normal of four.

The summary of groups I to IV, inclusive, is given in table 1.

Group A In 20 of 28 counts, or 71 per cent, the percentage of polymorphonuclear neutrophils was increased above the normal 68. The nonfilament count was the least in group A. In 23 of 28 counts, or 82 per cent, the percentage of lymphocytes was less than the normal of 25. The percentages of eosinophiles and basophiles were all within normal range.

Group B The findings for this group were practically the same as for groups A, C, and D.

Group C The average leukocyte count was the lowest of those in groups A to D, inclusive, in only one case being increased to more than 10,000 cells per cubic millimeter of blood. In only 33 per cent of the counts was the average percentage of polymorphonuclear neutrophils above normal. The shift to the left or nonfilament count was slightly increased to 12 cells in 200. In two counts the percentage of lymphocytes was increased above

TABLE I

Summary of Average Leukocyte Counts in Groups I to IV, Inclusive

Group	Cases	Duration, years *	Leukocytes, per cubic millimeter	Nonflament count, per cent	Differential count, per cent				
					Polymorphonuclear neutrophils	Lymphocytes	Monocytes	Eosinophiles	Basophiles
I	15	1/2 or less	7,693	8.1	63.8	27.2	5.9	1.9	0.7
II	11	1/2 to 1	7,307	9.2	71.0	18.7	8.4	1.6	0.3
III	9	1 to 2	11,055	16.0	75.3	14.8	7.2	1.8	0.6
IV	5	2 to 13	6,940	12.3	69.8	18.8	7.0	3.8	1.0

* Exact limits of the groups are given in the text

30, whereas in the others, with the exception of one case, it was practically within normal limits. The percentage of monocytes was increased in four counts whereas the average percentage was normal. The percentages of eosinophiles and basophiles were both within normal limits.

Group D The average percentage of polymorphonuclear neutrophils was normal, however, in 13 of 21 counts, or 61 per cent, the percentage of polymorphonuclear neutrophils was slightly increased. The shift to the left was not marked. The average percentage of lymphocytes was slightly below normal, with 66 per cent of the counts being below 25. While the average monocyte count was normal, the percentage was increased above normal in 29 per cent of the counts. In two instances the percentage of eosinophiles was increased above the normal limits while the percentage of basophiles was normal.

The summary of groups A to D, inclusive, is given in table 2.

Cases of Lymphosarcoma The findings in cases of lymphosarcoma differed only slightly from those in cases of Hodgkin's disease. In two cases in this group the leukocyte count was above 8000 per cubic millimeter. In 23.5 per cent of the counts the percentage of polymorphonuclear neutrophils was increased above normal. Of the lymphocyte counts, 41 per cent were below normal, 29 per cent above normal. There was also an increase above normal in 18 per cent of the monocyte counts. In two counts, or 11 per cent, the percentage of eosinophiles was increased above normal. The basophile counts were increased in two instances.

COMMENT

From this study it appears that there is no specific morphologic blood picture diagnostic of Hodgkin's disease. Estimations of the number of

TABLE II
Summary of Average Leukocyte Counts in Groups A to D, Inclusive

Group	Extent of involvement	Cases	Leukocytes, per cubic millimeter	Nonfilament count, per cent	Differential count, per cent				
					Polymorphonuclear neutrophils	Lymphocytes	Monocytes	Eosinophiles	Basophiles
A	Cervical, supraclavicular, or axillary (1 node) *	17	8,218	63	71.6	18.1	7.5	2.2	0.6
B	Inguinal (1 node)	5	10,480	17.0	74.6	17.6	5.9	1.4	0.4
C	Cervical, supraclavicular, or axillary (2 nodes) †	6	5,950	12.0	61.8	28.1	6.7	1.8	0.6
D	General adenopathy	12	8,517	9.3	67.5	22.6	6.8	2.4	0.7

* Only one node affected in any of these three situations

† Two nodes affected in one of these situations or one node in each of two of these situations, namely, two cervical nodes, or one cervical and one axillary node, and so forth

leukocytes per cubic millimeter of blood showed them to be within normal limits, as were also the various percentages in the differential counts (group I, table 1). It is true that in an occasional case there was a deviation from the normal of slight degree, but this in itself is without significance as the averages of the group were well within those recognized as normal. In group II, however, in which Hodgkin's disease was of slightly longer duration, there was definite polymorphonuclear leukocytosis with a decrease in the number of lymphocytes, as has been observed by other investigators. In these groups I and II there was no tendency toward a shift to the left of the neutrophils, the values being well within normal limits, that is, 8.1 and 9.2 nonfilamented cells, respectively, per 100 neutrophils.

In group III, in which the duration of the disease was longer, the most definite changes occurred. There was a definite but slight increase in the number of polymorphonuclear neutrophils, a relative decrease in the number of lymphocytes, and an increase in the number of nonfilamented neutrophils. This is probably due to the more widespread involvement of the body by the process, with inroads of sufficient degree to produce toxic changes. Yet in group IV, in which the disease was of longer duration, such results are not found. This in itself seems at first sight to contradict the conclusions for group III, but in an individual who has had the disease for more than two years there is probably a good deal of natural resistance to the process, it may be growing slowly and therefore not produce much general effect on the peripheral blood. On the other hand, the process may

be in a terminal stage and by reason of this prevent a normal reaction of the hematopoietic elements in the peripheral blood

It is of interest that in this series of cases the most marked changes in the blood were seen in cases of inguinal adenopathy (group B). It is probable that in such cases there was associated involvement of the abdominal and pelvic retroperitoneal nodes, resulting in more widespread involvement than would be expected, consequently, more change in the cellular elements of the peripheral blood might have occurred. It is difficult to understand why individuals with generalized adenopathy (group D) should not present more changes in the cells of the blood, for as shown in table 2 this group has, on the average, leukocytes and individual cells in normal numbers. Apparently the extent of involvement of the process has but little effect on the changes in the blood.

Monocytosis did not occur in any of the groups, which is in accord with the conclusions of recent investigators in this subject. The individual cells have a greater tendency to be indented (shift to the right) than normal, but as this may occur in many other conditions it is without diagnostic significance.

Polymorphonuclear leukocytosis is not a constant finding but was present in this series in cases in which the disease had been present for more than one year and less than two years. The absence of polymorphonuclear leukocytosis in earlier cases would be contradictory evidence for the thesis that Hodgkin's disease has its origin in an infectious process.

SUMMARY AND CONCLUSIONS

The analysis of the findings in 40 cases of Hodgkin's disease revealed that leukocytosis of slight degree was present in cases in which the disease was of between one and two years' duration. Polymorphonuclear neutrophils were slightly increased in the differential count in cases in which the disease was of six months' duration or longer. A slight relative decrease in the number of lymphocytes occurred in the same cases. The monocytes showed a greater tendency toward a shift to the right than occurs in normal individuals. Extensiveness of the disease apparently does not produce more marked changes in the blood. There is no specific change in the leukocyte picture which is diagnostic of Hodgkin's disease.

In the nine cases of lymphosarcoma, the average percentage of polymorphonuclear neutrophils was slightly decreased and the average percentage of lymphocytes slightly increased as compared with the results in cases of Hodgkin's disease. The percentages of other leukocytes and the total leukocyte count were nearly the same as they were in cases of Hodgkin's disease.

BIBLIOGRAPHY

1. HODGKIN, T. On some morbid appearance of the absorbent glands and spleen, *Trans Medico-Chir. Soc. Edinburgh*, 1832, **xvii**, 68-114.

- 2 FABIAN, ERICH Über den Blutbefund der Lymphogranulomatosis (Paltaut-Sternberg) nebst Bemerkungen über die Blutveränderungen bei der Lymphsarkomatosis und der Lymphdrüsentuberkulose, *Wien klin Wchnschr*, 1910, *xxiii*, 1515-1519
- 3 BUNTING, C H The blood-picture in Hodgkin's disease, *Bull Johns Hopkins Hosp*, 1911, *xxii*, 369-372
- 4 BUNTING, C H The blood-picture in Hodgkin's disease (second paper), *Bull Johns Hopkins Hosp*, 1914, *xxv*, 173-177
- 5 YATES, J L A clinical consideration of Hodgkin's disease, *Bull Johns Hopkins Hosp*, 1914, *xxv*, 180-194
- 6 LONGCOPE, W T, and McALPIN, K R Hodgkin's disease, 1920, *Oxford Medicine*, vol 4, pt 1, 1-43
- 7 McALPIN, K R Blood counts in Hodgkin's disease, *Arch Int Med*, 1923, *xxxi*, 954-957
- 8 WEISS, J Das Leukozytenbild der Lymphogranulomatose, *Wien klin Wchnschr*, 1924, *xxxvii*, 389-391 Leukocytes in lymphogranulomatosis, *Abstr In Jr Am Med Assoc*, 1924, *lxxxii*, 1743
- 9 FALCONER, E H The blood picture in Hodgkin's, *Calif and West Med*, 1930, *xxxi*, 83-87
- 10 STRAUBE, GUNTHER Über das Blutbild der Lymphogranulomatose, *Folia haematol*, 1931, *xiv*, 125-136
- 11 KERNOHAN, J W Personal communication to the authors

THE INTERRELATIONSHIP OF GASTROINTESTINAL AND RENAL DISEASE *

By HARRY GAUSS, F A C P , *Denver, Colorado*

CLINICALLY disease of the kidney and disease of the gastrointestinal tract are clearly differentiated in a majority of the cases. Frequently, however, the various types of renal disease give rise to symptoms referred mainly or even exclusively to the gastrointestinal tract. In a majority of these cases a careful examination will reveal the source of the disturbance. In some instances, however, severe gastrointestinal distress alone may result from pathological changes in the urinary tract which are not detected in a routine examination. It is with this group of cases that this paper is concerned. The digestive disturbances are purely functional and clear up entirely when the underlying renal abnormality is corrected.

An explanation of the reference of symptoms between these two systems may be sought in their anatomic, neurologic, and metabolic relationships. The anatomic relationship may be summarized by pointing out that the anterior surface of each kidney is in close apposition to important structures forming part of the gastrointestinal system. On the right the kidney is in close vicinity to the liver, the duodenum, and the hepatic flexure of the colon, while on the left the kidney is in contact with the stomach, spleen, pancreas and descending colon. The innervations of both the digestive and urinary tracts are similar in that they contain autonomic fibers of both vagal and sympathetic type which have passed for the most part through the celiac plexus. From a metabolic point of view both the digestive tract and the kidney possess excretory functions. A definite balance exists as to the proportion of certain substances which will be excreted in the stools or in the urine. In case of renal failure an added excretory function may be laid upon the digestive glands.

In all these interrelationships must lie the secret of the functional disturbances so frequently set up in one system as a result of a disease process localized in the other. Of the exact mechanisms involved we are still quite ignorant. From the clinician's point of view, however, the following notes upon the incidence of such referred symptoms may be of practical value.

Anatomically almost the entire anterior surface of both kidneys is in close relationship with various parts of the digestive apparatus. They are separated from it by a layer of fatty areolar tissue, and by the peritoneum which in places forms folds or ligaments which extend to neighboring organs. Traction on the duodenorenal and nephrocolic ligaments is believed to be an important factor in the production of gastric symptoms (Himman, Longyear).

Both the kidneys and ureters and the gastrointestinal tract, including

* Read before the Eighteenth Annual Clinical Session of the American College of Physicians, Chicago, Illinois, April 20, 1934

the liver, gall-bladder and pancreas, derive their nerve supply from almost the same sources the vagus and the sympathetic fibers from the celiac plexus

To a lesser extent pathological conditions in either system may affect the other through alterations in the chemical composition of the blood and body fluids which they may bring about This is seen most strikingly in the digestive disturbances so common in uremia

Hydronephrosis Hydronephrosis from various causes is frequently associated with gastrointestinal symptoms Renal symptoms may be slight or absent, and there may be no abnormality in the urine when tested

The difficulty in differentiating renal and gall stone colic is well recognized Forman calls attention to the following signs and symptoms which suggest a renal origin there is reflex rigidity of the lumbar muscles, the pain is radiated caudad, bile does not appear in the urine, blood or pus may be present in the urine, although between attacks the urine may be normal, bimanual examination may elicit tenderness in the kidney area, and roentgen-ray may show evidence of renal disease, such as stone, stricture, hydronephrosis, etc

Movable Kidney Morrissey regards the production of gastrointestinal symptoms in movable kidney as the result of direct traction on the gastrointestinal tract Traction, he believes, is exerted on the second portion of the duodenum through its areolar tissue connection with the right kidney The lack of mesentery prevents it from moving forward, so that it is stretched and its lumen becomes diminished Interference with the digestive current and secondary dilatation of the stomach follow, while at the same time, the bile ducts are elongated and narrowed, and the passage of bile through them is interfered with On the left side similar disturbance of digestion may follow the pull of the kidney on the stomach and colon

Nephrocoloptosis Longyear believes that the kidney alone cannot exert sufficient traction on the gastrointestinal tract to produce symptoms, but that the combined ptosis of kidney and colon can initiate gastrointestinal symptoms In the production of these symptoms the nephrocolic ligament plays an important part Four factors, he states, are necessary for the occurrence of nephrocoloptosis, namely (1) a weak or absent hepatocolic ligament, (2) a loose kidney attachment at its hilum and to Gerota's capsule, (3) a strong and short nephrocolic ligament, and (4) a prolapse of the cecum and ascending colon Nephrocoloptosis occurs commonly on the right side but rarely on the left side, the reason being that on the right side the hepatocolic ligament, which helps to support the ascending colon, may be weak or absent, while on the left side the phrenocolic ligament, which supports the descending colon at the splenic flexure, is always present Further, it is uniformly strong and dependable, and so prevents the downward displacement of the gut at this point Fowler believes that ptosis of the adrenal gland is also a factor in producing this syndrome

In nephrocoloptosis there is traction on the duodenum, causing angulation of the bowel and interference with the function of the biliary and pan-

creatic ducts The symptoms are commonly gastrointestinal in character rather than renal The patients complain of indigestion, distress after eating, gas eructations, nausea, constipation, flatulence, pain in both hypochondria which is either dull or colicky, and pain in the right lower quadrant For treatment Longyear recommends an abdominal support, and also the surgical operation of nephrocolopexy which fixes both the kidney and colon

Not all writers agree that ptosis of the kidney is always secondary to ptosis of the colon According to Hinman, most authorities believe that the majority of surgical nephroptoses are not accompanied by enteroptosis, and that not all cases of visceroptosis are accompanied by nephroptosis

Ureteral Stricture Ureteral stricture is one of the diseases of the urinary tract which are most frequently associated with gastrointestinal disturbances We owe to Hunner credit for demonstrating the relatively frequent occurrence of this condition

Ureteral stricture may be of congenital or acquired origin The acquired form which predominates is attributed to focal infection, infectious disease, or traumatism

The symptomatology is variable In one group of cases attention is directed at once to the urinary tract by attacks of ureteral colic These are attributed by Watkins and Cumming to sudden occlusion of the ureter by edema of the strictured area

In a much larger group the symptoms are so diverse and so predominantly gastrointestinal in character that without painstaking study the stricture may be overlooked Thus in a series of 50 cases reported by Dabney severe digestive disturbances occurred in over 75 per cent, and pain referred to the right lower quadrant occurred in 34 per cent

Pain is the most frequent symptom of ureteral obstruction It varies in character from a constant dull nagging ache to a sharp violent paroxysmal pain This may be present in the right lower quadrant, or it may be diffuse over the entire abdomen, and not referred to the urinary tract Other symptoms frequently met with include indigestion, anorexia, nausea, vomiting, headache, flatulence, diarrhea, and rectal pain Hunner emphasizes that careful inquiry will often elicit a history of occasional slight irritability of the bladder, or frequent micturition, particularly when nervous or excited, or at the menstrual period, or in association with a cold Painful coitus may be complained of

Urine analysis is not always helpful Hunner found in 20 per cent of his cases a chronic pyelitis with characteristic abnormalities in the urine In 50 per cent minor abnormalities were found a few erythrocytes, a few leukocytes, albumin in varying amounts, or casts, or a combination of these elements In 30 per cent the urine was normal

Physical examination may reveal tenderness on bimanual palpation over the kidney region, or on pressure over the point where the ureter crosses the pelvic brim, approximately one and a half inches lateral to and below the umbilicus This may elicit pain which radiates to the bladder On vaginal

examination pressure over the ureters in the broad ligament above the bladder may cause tenderness or pain which may be recognized by the patients as identical with that with which they are familiar

Difficulties often arise in the differentiation of chronic appendicitis from ureteral stricture. As Dabney has emphasized, both conditions are characterized by a chronic course, by a tendency to digestive disturbances and constipation, by pain in the right lower quadrant of the abdomen, and by the fact that exercise is not well borne. In both there is often tenderness in the right lower quadrant, and occasionally a slight elevation of the temperature and leukocyte count, while the urine may show no abnormality. Whenever there is a reasonable possibility of ureteral stricture a urologic examination should be carried out, including ureteral catheterization and a urogram.

CASE REPORTS

The following case reports illustrate some instances of renal disease that presented essentially gastrointestinal symptoms.

Case 1 Renal Tuberculosis with Stricture of the Right Ureter Miss M. M., aged 26, complained of loss of appetite, gas pains, excessive flatulence, bilious spells, dizziness, loss of strength, and inability to gain weight, all of which were several years in duration.

Physical examination showed an asthenic young white woman, 102 pounds in weight, 5 feet 5 inches in height, pulse 90, temperature 98, respiration 14, blood pressure systolic 105, diastolic 65, who was not acutely ill. The eyes reacted to light and to accommodation. The heart was not enlarged and the sounds were clear. The lungs were normal. The liver and spleen were not palpable. The descending colon was spastic, palpable and tender. There was vague abdominal distress in the entire lower abdomen which was not clearly localized. A pelvic examination was not made.

The blood count showed a moderate secondary anemia. The urine was quite normal, there was only an occasional leukocyte and an occasional epithelial cell present. The basal metabolic rate, Ewald test meal and stool examinations all were normal.

Roentgen-ray showed normal lung fields, dropped type heart, ptosis and spasticity of the colon.

The diagnosis at this time was Undernutrition of 31 pounds, secondary anemia, visceroptosis, spastic colon. There was no evidence of tuberculosis and little reason to suspect it.

On a full diet she gained 12 pounds during the next two months, and the digestive symptoms subsided.

However in the third month she complained of polyuria and dysuria. The urine at this time contained large numbers of leukocytes and acid-fast bacilli which, on guinea pig inoculation, proved to be tubercle bacilli. The lungs again showed no evidence of tuberculosis on physical and roentgenoscopic examination. Cystoscopic examination by Drs. T. L. Howard, J. M. Lipscomb and J. E. Hartley revealed that the left kidney was normal and that the leukocytes and acid-fast bacilli came from the right kidney. A catheter encountered a stricture a short way up the right ureter. The kidney was subsequently removed by Drs. Howard, Lipscomb and Hartley and the patient made an uneventful recovery.

Comment This patient probably had a renal tuberculosis at the time she presented herself for examination. However there were no external

manifestations of the disease. The symptoms she presented were essentially gastrointestinal, and the urine was entirely normal. When the focus of tuberculosis in the kidney broke through into the urine, the diagnosis became apparent.

Case 2 Stone in Left Ureter. Mr. M. D., aged 22 years, complained of attacks of indigestion which came on at irregular intervals over a period of several months. During these attacks he had severe pain in the left lower quadrant of the abdomen, he was nauseated, had a distaste for food, usually had a diarrhea. The attacks were completely relieved by bromides. Between attacks he felt well, but was very nervous and high strung. He had been examined in a large clinic, and prostatic massage had been advised.

Physical examination showed a well nourished young man, weighing 138 pounds, 5 feet 8 inches in height, pulse 78, respiration 14, temperature 98, blood pressure 115 systolic and 80 diastolic. The eyes reacted to light and to accommodation. The throat and mouth were normal. The heart and lungs were approximately normal. The liver and spleen were not palpable. The descending colon was spastic, palpable and tender. There was tenderness on the left side of the abdomen which seemed to correspond more or less with the descending colon. The reflexes were present, equal and exaggerated. The blood count, Ewald test meal and urine were normal. The urine contained no blood, no albumin, only an occasional leukocyte.

Roentgen-ray of the gastrointestinal tract showed a spasticity of the descending colon, otherwise it was normal.

At this time, a diagnosis of spastic colon was made. There are no symptoms referable to the urinary tract, no polyuria, no dysuria, no pain in lumbar region or the genitals.

Several months later the patient had a sharp attack of pain, more severe than any of the preceding attacks. The attack was located in the lumbar muscles as well as in the abdomen, and it radiated down the leg. The urine at this time contained large numbers of erythrocytes, and the roentgen-ray showed a small stone in the left ureter which had not been discovered in any of the previous examinations. The stone was removed by transureteral manipulation. The patient has been free from symptoms for two years.

* The small ureteral stone was undoubtedly present at the time the patient presented himself for examination, though it did not at first elicit the characteristic symptoms commonly associated with that type of lesion. In this case, only the appearance of the ureteral colic led to a correct diagnosis.

Case 3 Chronic Pyelitis with Stricture of Left Ureter. Mr. H. C. complained of attacks of severe pain coming on after eating. The pains were located in the right upper quadrant of the abdomen in the region of the liver. The pain was sharp, paroxysmal, colicky, it spread to the entire abdomen, and was so severe that it required sedative medication for relief. These attacks had been coming on about once a week for two months. The attacks commonly came on about one half hour after eating. Between attacks he was free of pain, but felt tired and languid, he had no strength and had lost some weight. He was troubled with excessive gas, belching and flatulence.

Physical examination showed a white male of 140 pounds, 5 feet 6 inches in height. His pulse was 72, the temperature 97, the respiration 15, the systolic blood pressure 130, and the diastolic 67. He was not acutely ill at the time he was seen. The eyes reacted to light and to accommodation. The tonsils were enlarged but not infected. The heart and lungs were approximately normal. The abdomen did not relax well. There was marked tenderness in the right upper quadrant, particularly along the costal margin. The entire right side of the abdomen was spastic. There

was some tenderness over the cecum. The reflexes were present, equal and exaggerated.

Roentgen-ray of the stomach, intestines and gall-bladder showed all of them to be normal.

The blood count gave a leukocyte count of 18,400. The Ewald test meal was normal, and the urine was loaded with pus cells and colon bacilli, but was free from bile. The stool contained the normal bile pigments. Cystoscopic examination showed the left kidney and ureter to be normal, the pus came from the right kidney, and a stricture was encountered in the ureter.

Diagnosis: Pyelitis, right side, with stricture of ureter.

This patient was seen through the courtesy of Dr. Maurice Levy of Denver.

The diagnosis in this patient presented little difficulty because examination of the urine indicated at once an involvement of the renal system. The case is of interest because all the symptoms were gastrointestinal in character and suggested a gall stone colic. The patient never mentioned a single symptom referable to the urinary system, and it was only on subsequent interrogation that the patient recalled that years previously he had had trouble with his kidneys.

SUMMARY

1 While renal disease and disease of the gastrointestinal tract can usually be differentiated clearly, in a small group of cases the symptoms are confusing and may lead to errors in diagnosis.

2 The renal and gastrointestinal systems are related anatomically through their juxtaposition and their ligamentous attachments, and neurologically through their common innervation.

3 The following renal disorders have been reported as being common sources of gastrointestinal symptoms: stricture of the ureter, hydronephrosis, movable kidney, pyelitis, stone.

4 In these conditions examination of the urine may reveal no definite abnormality and therefore be of no aid in diagnosis.

5 Physical examination may be helpful in eliciting characteristic pain or tenderness on palpation of the kidneys or the ureters where they cross the pelvic brim, or at their lower ends within the broad ligaments.

6 A definite diagnosis can usually be established by means of ureteral catheterization and urograms.

REFERENCES

- BENCE-JONES, H. Philos. Trans. Roy. Soc. London, 1845, CXXX, 335. Cited by FISK, C. J. Observations on the "alkaline tide," after meals, Jr. Biol. Chem., 1921, XLIV, 163.
- BRAASH, W. F. Stricture of ureter, Jr. Am. Med. Assoc., 1928, LCI, 1263-1268.
- CUNNINGHAM, D. J. Textbook of anatomy, 4 Ed., 1909, Wm. Wood & Company, N. Y.
- DABNEY, M. Y. Differential diagnosis of ureteral stricture and chronic appendicitis, South. Med. Jr., 1924, XVII, 439-444.
- ELWYN, H. Some present day concepts in nephritis, Am. Jr. Med. Sci., 1930, CLXXX, 149-166.
- FORMAN, J. Renal factor in evaluating the patient with chronic gastrointestinal symptoms, Internat. Clin., 1929, II, 64-80.

- FOWLER, O S Effect of general visceroptosis upon adrenal gland, Urol and Cutan Rev, 1933, *xxxvii*, 519-526
- FRIEDENWALD, J, and MORRISON, S Relation between gastric and renal disease, Jr Am Med Assoc, 1932, *xciv*, 524-529
- GINSBERG, H M Symptoms of ureteral obstruction and their simulation of abdominal disease requiring operation, Med Jr and Rec, 1928, *cxxviii*, 211-213
- HFLWIC, F C, and SCHUTZ, C B Liver kidney syndrome, Surg, Gynec and Obst, 1932, *lv*, 570-580
- HINMAN, F Renal structure and function (*In* Nelson's Loose-Leaf Living Surgery, Vol 6 1928, Thomas Nelson and Sons, New York)
- HOWARD, H W, and LeCOCQ, M Chronic ureteritis, Northwest Med, 1927, *xxvi*, 154-157
- HUBBARD, R S Association of renal and gastric disorders with constancy of urinary reaction, Jr Clin Invest, 1930, *ix*, 37-41
- HUNNER, G L Ureteral stricture etiology, diagnosis, pathology and treatment of new abdominal syndrome, Am Jr Med Sci, 1927, *clxxiii*, 157-164
- JFLIFFE, S E, and WHITE, W A Diseases of the nervous system, 1923, Lea and Febiger, Philadelphia
- KFLLY, H A, and BURNAM, C F Diseases of the kidneys, ureters and bladder, 1914, D Appleton and Company, New York
- KUNTZ, A The autonomic nervous system, 1929, Lea and Febiger, Philadelphia
- LONGYEAR, H W Nephrocoloptosis, 1914, C V Mosby Company, St Louis
- MORRISSEY, J H Renal factor in chronic gastrointestinal symptomatology, Rhode Island Med Jr, 1928, *xi*, 71-76
- SAMUELS, A, and KERN, H Hydronephrosis with gastrointestinal symptoms, Urol and Cutan Rev, 1926, *xxv*, 644
- WATKINS, J T, and CUMMING, R E Significance of ureteral stricture in relation to abdominal and other symptoms, ANN INT MED, 1928, *i*, 707-728

FURTHER OBSERVATIONS ON THE CAROTID SINUS REFLEX

By LOUIS H SIGLER, M D , *Brooklyn, N Y*

IN previous communications^{1, 2, 3} I reported the incidence and the degree of cardiac slowing induced by the carotid sinus reflex in a series of 345 cases. The cases were divided into five groups as follows: Group I, coronary artery disease with definite myocardial damage, Group II, hypertension and hypertensive heart disease, Group III, rheumatic heart disease, Group IV, individuals with cardiac symptoms but no demonstrable cardiac disease, Group V, general constitutional disease (non-cardiac).

It was shown that the order of frequency and degree of response were Groups I, II, III, V and IV—the first showing the highest frequency and degree of response and the last the lowest. Males showed a higher frequency and degree of response than females, and there was an increase in frequency of response with advancing age.

The present communication deals with an analysis of 426 additional cases, consisting of 243 males and 183 females. These were all ambulatory cases, most of whom had cardiovascular disease.

The grouping of this series was as follows: Group I, arteriosclerotic heart disease, Group II, hypertension and hypertensive heart disease, Group III, arteriosclerotic and hypertensive heart disease, Group IV, rheumatic heart disease, Group V, psychoneurotic heart disturbances, Group VI, heart disturbances or disease of various other causes, and, Group VII, cases without cardiovascular disease. This finer subdivision was adopted in order to see how the carotid sinus reflex exhibits itself in more precise types of disease.

As in the previous paper only the cardio-inhibitory part of the carotid sinus reflex is reported. The vasomotor depressor effect of the reflex, exhibited by fall in blood pressure, and the other reflex effects induced by the carotid sinus pressure were not studied.

DETAILED ANALYSIS OF CASES IN THIS SERIES

Group I consists of 113 cases, 96 males and 17 females. All showed clinical evidence of general arteriosclerosis and coronary sclerosis of various degrees. In the majority of cases the electrocardiogram corroborated the presence of myocardial involvement. Many cases also had aortic sclerosis. Besides coronary disease, three cases had chronic bronchitis and emphysema, one Menier's syndrome, one congenital patent ductus arteriosus, three neurocirculatory asthenia, two diabetes mellitus, six obesity, one pulmonary tuberculosis, and three chronic cholecystitis and cholelithiasis.

* Received for publication December 14, 1935

In 10 cases there was a history of recent or past coronary occlusion, which in one instance was followed by pulmonary embolism

Group II consists of 45 cases, 14 males and 31 females. Although all showed more or less cardiac hypertrophy secondary to hypertension, none had gross evidence of insufficiency of the coronary circulation. In three cases the hypertension was of nephritic origin. In the rest it was of the so-called essential type. Fourteen cases showed marked obesity, six cases had definite psychoneuroses, two had chronic arthritis, one psoriasis, three cholecystitis and cholelithiasis, and one early multiple sclerosis.

Group III consists of 89 cases, 50 males and 39 females. All gave a history of hypertension and showed more or less hypertension at the time of the examination. All showed evidence of more or less general arteriosclerosis and coronary sclerosis. In addition, two had evidence of nephrosclerosis with early renal insufficiency. All had evidence of aortic sclerosis with more or less marked dilatation. Twelve cases showed considerable obesity, six gave a history of past coronary occlusion, four cases were diabetic, three showed psychoneurotic symptoms and three showed symptoms attributable to the menopause.

Group IV consists of 43 cases, 19 males and 24 females with chronic rheumatic heart disease. Fifteen showed mitral stenosis, one with auricular fibrillation, 16 had mitral insufficiency and mitral stenosis, four of whom had auricular fibrillation, two had mitral stenosis, mitral insufficiency and aortic insufficiency, three aortic insufficiency and stenosis, one aortic stenosis and mitral stenosis, three aortic insufficiency, three had mitral insufficiency. In addition two had hypertension, one chronic bronchitis, and one showed evidence of hyperthyroidism.

Group V consists of 23 cases, 10 males and 13 females with various cardiac manifestations of psychoneurotic origin. Care was taken to exclude from this group definite organic cardiac disease. All symptoms referable to the heart were entirely subjective. If objective findings were present, such as murmurs, various tachycardias and arrhythmias, they could invariably be considered to be functional in type.

Group VI consists of 52 cases, 26 males and 26 females. Some presented abnormal cardiac signs and symptoms of such character that the diagnosis of heart disease could not be made with certainty. Others had distinct heart disease of unknown etiology. Still others had cardiovascular disease of known etiology, but because they were relatively few in number no separate groups were made of them. Thus there were six cases of syphilitic aortic disease with reactive cardiac changes, six with thyrotoxic heart disease, two with congenital heart disease, one of chronic myelogenous leukemia with suspicious cardiac involvement, one secondary to marked chronic pulmonary lesions. Some cases might have been classed as neurocirculatory asthenia, but there was evidence suggesting early cardiovascular disease of arteriosclerotic origin.

Group VII consists of 61 cases, 28 males and 33 females. It includes cases of obesity, neurasthenia, menopause, gastric and duodenal ulcers,

anemias, diabetes, Hodgkin's disease, and so on. None showed clinical evidence of cardiovascular disease, although in a few, premature contractions or other cardiac abnormalities were observed, which could be attributed to reflex disturbances.

CARDIAC RESPONSE TO THE CAROTID SINUS REFLEX

In a previous report¹ a separate analysis was made of the reflex cardiac response to right and left carotid sinus pressure, and to combined right and left pressure. Some individuals exhibited only a right pressure response, others a left, but most showed a bilateral response. The degree of response varied for the two sides in many individuals.

In this series, in order to simplify the results, only the maximum response was used to classify each case. This, as before, was obtained on right or left carotid sinus pressure or equally on both sides.

TABLE I
Response to Carotid Sinus Pressure among Males and Females

Groups	Total No. Cases		Total Not Responding		Total Responding and Percentage Response			
	Males	Females	Males	Females	Males		Females	
					No.	%	No.	%
I	96	17	18	4	78	81.2	13	76.5
II	14	31	2	7	12	85.7	24	77.4
III	50	39	8	13	42	84	26	66.6
IV	19	24	4	10	15	78.9	14	58.3
V	10	13	4	8	6	60	5	38.4
VI	26	26	8	13	18	69.2	13	50
VII	28	33	6	12	22	78.5	21	66.6
Total	243	183	50	67	193	79.4	116	63.3

Group I—Arteriosclerotic heart disease

Group II—Hypertensive heart disease

Group III—Arteriosclerotic and hypertensive heart disease

Group VII—General constitutional disease (non-cardiac)

Group IV—Rheumatic heart disease

Group V—Psychoneurotic heart disease

Group VI—Other forms of heart disturbances and disease

Table 1 and figure 1 represent the response of this series of 426 cases. An analysis of the figures shows that the greatest frequency of response is in the hypertensive and in the arteriosclerotic and hypertensive groups. Rheumatic heart disease occurs next in frequency as does the non-cardiac group. The least response is seen in psychoneurotic heart disturbances and in the miscellaneous group of heart abnormalities. The latter shows a somewhat higher frequency of response than the psychoneurotic group. In all groups, females showed a definitely lower frequency of response than males.

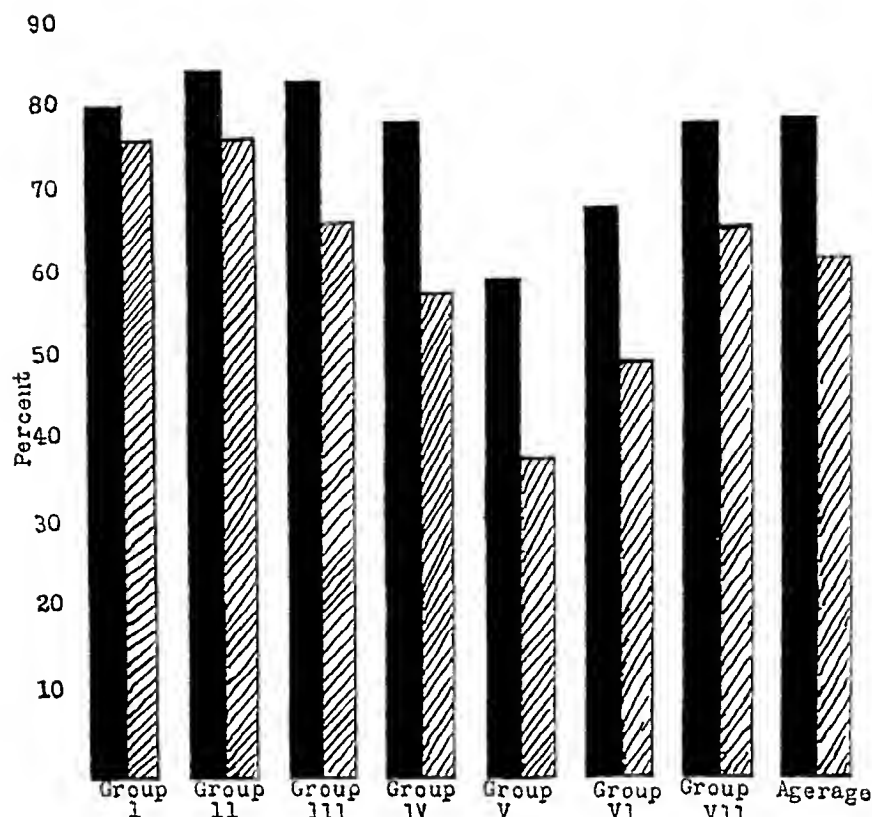


FIG 1 Percentage response to vagal stimulation Black column represents males, light column represents females Ordinates represent percentage response, abscissae represent disease groups

TABLE II
Degree of Slowing in the Various Groups

Groups	+				++				+++				++++			
	Males		Females		Males		Females		Males		Females		Males		Females	
	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%	No of Cases	%
I	11	14.1	4	30.8	16	20.5	3	21.3	22	28.2	2	15.3	29	37.2	4	30.8
II	5	41.7	9	37.5	6	50	6	25	1	8.3	5	20.8	—	—	4	17.5
III	10	23.8	8	30.8	13	30.9	9	34.6	8	19.1	4	15.3	11	26.2	5	19.3
IV	4	26.6	7	50	4	26.6	4	28.5	4	26.6	3	21.5	3	20	—	—
V	—	—	2	40	1	16.6	2	40	4	66.6	—	—	1	16.6	1	20
VI	—	—	1	7.6	9	50	7	53.8	6	33.3	4	30.7	3	16.7	1	7.6
VII	6	30.0	6	23.5	6	30.0	10	47.6	5	25.0	4	19	3	15.0	1	4.9
Total	36	18.8	37	31.9	55	28.8	41	35.4	50	26.2	22	18.9	50	26.2	16	13.8

+ Slowing less than 25% of the original rate

++ 25% to 50%

+++ 50% to short stoppage of heart

++++ Where the heart stopped for more than two seconds

Group I—Arteriosclerotic heart disease

Group II—Hypertensive heart disease

Group III—Arteriosclerotic and hypertensive heart disease

Group IV—Rheumatic heart disease

Group V—Psychoneurotic heart disease

Group VI—Other forms of heart disturbances and disease

Group VII—General constitutional disturbances (non-cardiac)

Degree of Slowing In the previous report, slowing of the heart under the carotid sinus reflex was divided into three degrees—those showing less than 25 per cent slowing as compared to original heart rate, those more than 25 per cent, and those where the heart stopped for at least two seconds. In

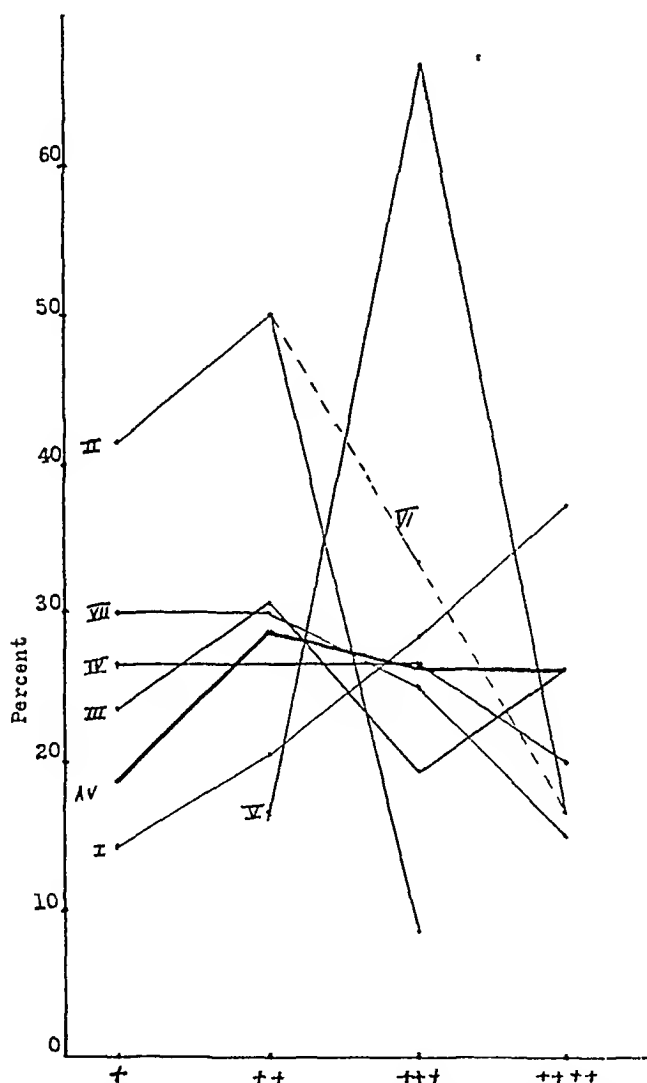


FIG 2 Degree of slowing among males. + Slowing less than 25 per cent of the original rate, ++ Twenty-five to 50 per cent, +++ Fifty per cent to short stoppage of heart, ++++ Where the heart stopped for more than two seconds. Disease groups are represented by Roman numbers. Ordinates represent percentage response in the various groups, abscissae represent the degree of response.

this series the degree of slowing was divided into four groups. Those showing less than 25 per cent slowing were designated as one plus, those showing 25 per cent to 50 per cent slowing as two plus, those showing 50 per cent slowing to temporary stoppage of the heart as three plus, and those where the heart stopped for more than two seconds as four plus. Table 2

and figures 2 and 3 show the degree of response of the various groups among males and females respectively

It will be seen that, with few exceptions, the tendency is for a greater percentage of cases to show the highest degree of slowing in the arterio-sclerotic group. In the hypertensive group this tendency appears to be in the opposite direction. It is also interesting to note that adding hypertension

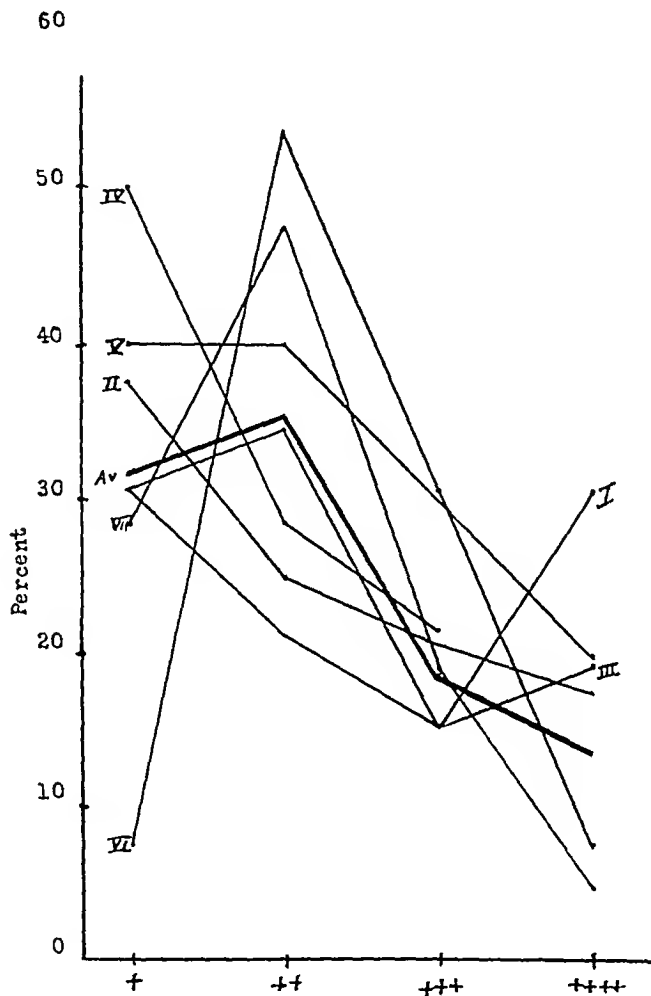


FIG 3 Degree of slowing among females. + Slowing less than 25 per cent of the original rate, ++ Twenty-five to 50 per cent, +++ Fifty per cent to short stoppage of heart, ++++ Where the heart stopped for more than two minutes. Disease groups are represented by Roman numerals. Ordinates represent percentage response in the various groups, abscissae represent the degree of response.

to arteriosclerosis has a tendency to lessen the degree of slowing. All other groups likewise show a tendency toward a lesser degree of slowing except in the psychoneurotic group. In this group, however, no conclusions may be drawn because of too small a number of cases.

There is a definite tendency for females to show a lesser degree of slowing. In cases with 4 plus response, females invariably showed a shorter

stoppage of the heart than males. In most of the females the stoppage was for no more than two seconds and the average was about 2.5 seconds. Most of the males, on the other hand, showed a stoppage of more than three seconds and the average was about four seconds. The longest stoppage occurred in severe forms of arteriosclerotic heart disease where in a few

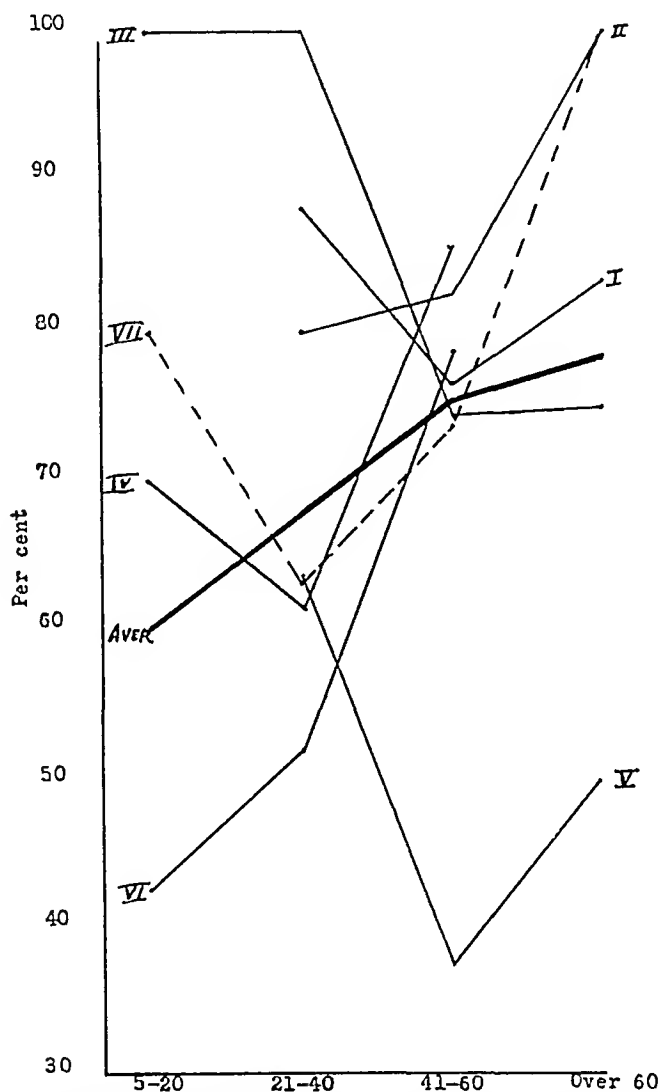


FIG 4 Percentage response of the cardio-inhibitory carotid sinus reflex at given ages for both sexes. Ordinates represent percentage response, abscissae represent age groups. Disease groups are represented by Roman numbers.

cases the heart stopped for 5 to 14 seconds. In the non-cardiac group, if the heart stopped it was never for more than two seconds, and that was produced only by strong pressure.

Response at Various Ages. Table 3 and figure 4 are an analysis of the response at various age groups in this series. Although the first age group is marked 5 to 20 years of age, there were only two cases less than 10 years

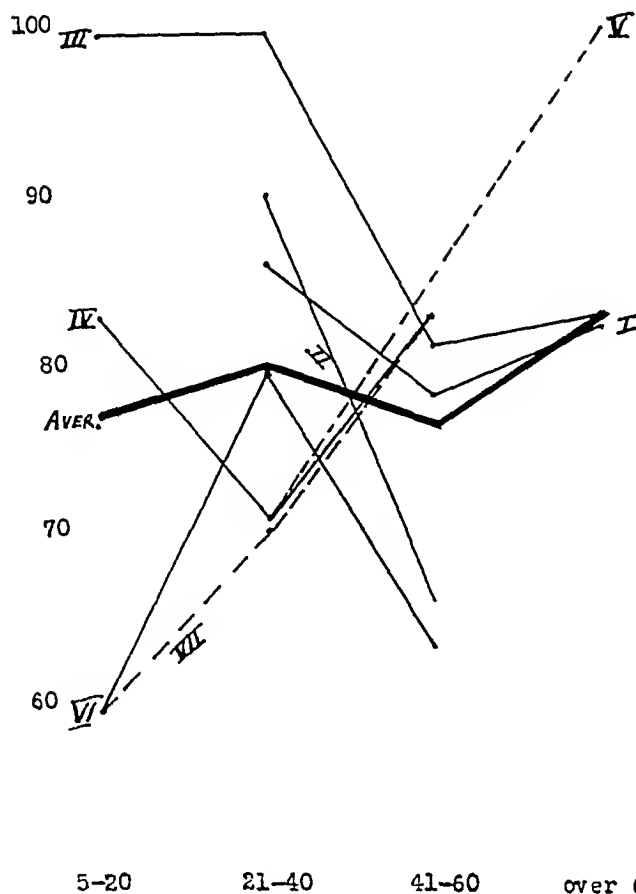


FIG 5 Percentage response of the cardio-inhibitory carotid sinus reflex at given ages for males. Ordinates represent percentage response, abscissae represent age groups. Disease groups are represented by Roman numbers.

TABLE III

The Cardio Inhibitory Carotid Sinus Reflex at Various Ages in the Various Groups
Males and Females

Groups	Ages 5-20 yrs			Ages 21-40 yrs			Ages 41-60 yrs			Ages over 60 yrs		
	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp
I	0	0	0.0	15	2	88.2	46	14	76.6	30	6	83.5
II	0	0	0.0	16	4	80.0	19	4	82.6	1	0	100.0
III	1	0	100.0	5	0	100.0	41	14	74.5	21	7	75.0
IV	7	3	70.0	16	10	61.5	6	1	85.7	0	0	0.0
V	0	2	0.0	7	4	63.6	3	5	37.5	1	1	50.0
VI	3	4	42.8	13	12	52.0	15	4	78.9	0	1	0.0
VII	4	1	80.0	19	11	63.3	17	6	73.9	1	0	100.0
Average	15	10	60.0	91	43	67.9	147	48	75.4	54	15	78.1

Disease groups are the same as in tables 1 and 2

of age, and three others less than 15 years All others were near to or actually 20 years old

With the exception of Groups III and V there is a definite increase in

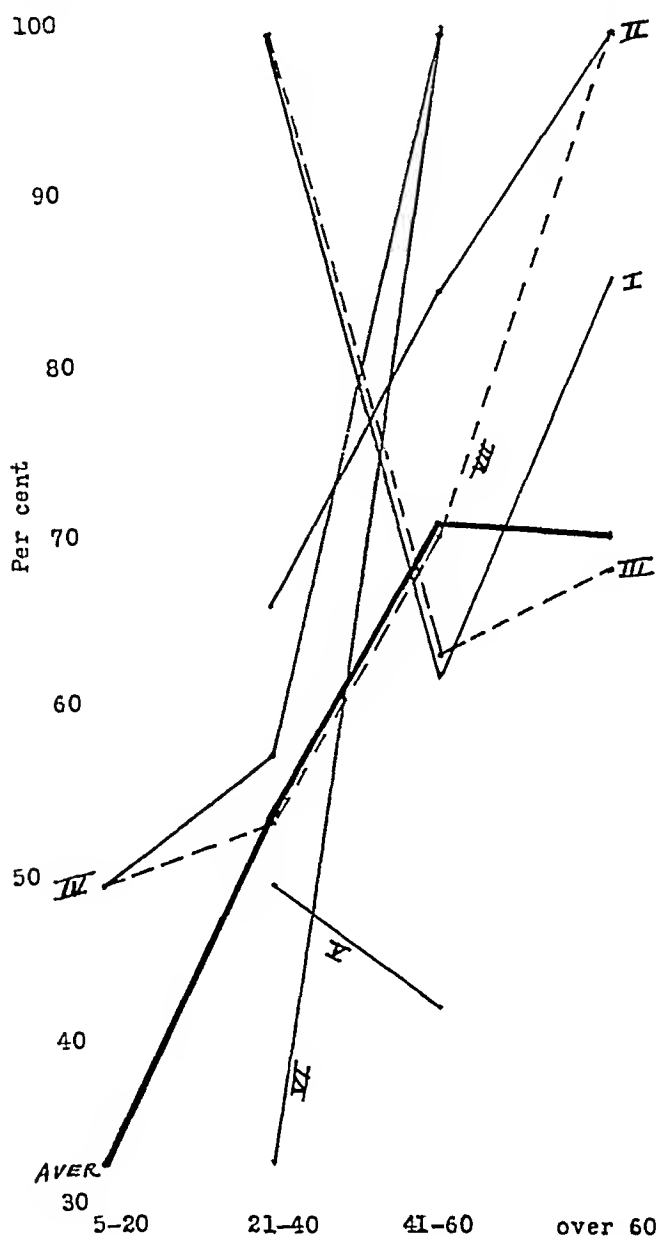


FIG 6 Percentage response of the cardio-inhibitory carotid sinus reflex at given ages for females Ordinate represent percentage response, abscissae represent age groups Disease groups are represented by Roman numbers

the incidence of response with advancing age In Group V the total number of cases was too small to permit the drawing of conclusions In Group III the number of cases in the early age groups is also too small for conclusions The findings, however, seem to point to the fact that the presence of arterio-

sclerosis and hypertension even early in life will increase the incidence of the cardio-inhibitory response to carotid sinus pressure

A separate analysis was made of the male and female age incidence of response Table 4 and figure 5 show the male response, and table 5 and figure 6 the female response

TABLE IV

The Cardio-Inhibitory Carotid Sinus Reflex at Various Ages in the Various Groups
Males

Groups	Ages 5-20 yrs			Ages 21-40 yrs			Ages 41-60 yrs			Ages over 61 yrs		
	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp
I	0	0	0 0	13	2	86 6	41	11	78 8	24	5	82 7
II	0	0	0 0	10	1	90 9	2	1	66 6	0	0	0 0
III	1	0	100 0	4	0	100 0	27	6	81 8	10	2	83 3
IV	5	1	83 3	5	2	71 4	5	1	83 3	0	0	0 0
V	0	1	0 0	5	2	71 4	0	1	0 0	1	0	100 0
VI	3	2	60 0	8	2	80 0	7	4	63 6	0	0	0 0
VII	3	2	60 0	12	5	70 5	5	1	83 3	0	0	0 0
Average	12	6	77 7	57	14	80 2	87	26	77 0	35	7	83 3

TABLE V

The Cardio-Inhibitory Carotid Sinus Reflex at Various Ages in the Various Groups
Females

Groups	Ages 5-20 yrs			Ages 21-40 yrs			Ages 41-60 yrs			Ages over 61 yrs		
	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp	Resp	Not Resp	% Resp
I	0	0	0 0	2	0	100 0	5	3	62 5	6	1	85 7
II	0	0	0 0	6	3	66 6	17	3	85 0	1	0	100 0
III	0	0	0 0	1	0	100 0	14	8	63 6	11	5	68 7
IV	2	2	50 0	11	8	57 8	1	0	100 0	0	0	0 0
V	0	1	0 0	2	2	50 0	3	4	42 8	0	1	0 0
VI	0	2	0 0	5	10	33 3	8	0	100 0	0	1	0 0
VII	1	1	50 0	7	6	53 8	12	5	70 5	1	0	100 0
Average	3	6	33 3	34	29	54 0	60	24	71 4	19	8	70 5

It will be seen that males have a tendency to show a greater incidence of response earlier in life than do females Females show a more regularly progressive increase in response with advancing age In males, on the other hand, the type of disease seems to be more important as a determining factor than the age The greatest *degree* of response occurred in later life, in each sex

DISCUSSION

It was well established by many investigators that stimulation of the carotid sinus induces two major independent reflexes—slowing of the heart and fall in blood pressure. Heymans⁵ found three other reflexes—a direct cerebral vascular reflex, changes in adrenalin secretion, and changes in respiration. That each one of these reflexes is independent of the others has likewise been well established. Thus Hering⁶ found that vagotomy and atropinization abolished the cardio-inhibitory reflex, while the fall in blood pressure could still be induced by carotid sinus pressure. Koch,⁷ Heymans,⁵ and various other observers have likewise demonstrated this point repeatedly.

The investigation reported in this paper as well as in the previous ones deals only with the cardio-inhibitory part of the carotid sinus reflex. Although slowing of the heart thus induced reflexly may to some extent be due to inhibition of the cardio-accelerator nerves as shown by Raginiers,⁸ and Bronk, Ferguson and Solandt,⁹ it is dependent predominantly upon reflex vagal stimulation, as evidenced by the effects of vagotomy and atropinization mentioned before.⁶ The cardio-inhibitory carotid sinus reflex response may then be considered to be an index of sensitivity of the vagus to reflex stimulation. This sensitivity varies in frequency and in degree. In normal individuals Sander¹⁰ found a fairly high incidence of response. The degree of response, in normal persons, however, is comparatively low.

Various forms of local and constitutional disease increase the incidence and degree of the vagal response. Hering,⁶ Koch,⁷ and Heymans⁵ attributed an increased response in some individuals to sclerosis of the carotid artery in the region of the sinus. This seems to have been disproved by Keele¹¹ who found no relationship between fall in blood pressure induced by carotid sinus pressure and localized sclerosis, in a series of 55 autopsy cases. Braun and Samet¹² found marked response associated with coronary disease. Danielopolu and Missirlin¹³ found an exaggerated reaction in chronic myocardial disease. Wenckebach¹⁴ likewise found it in association with cardiac disease. Various authors such as Koch, Hering, Heymans and others found that drugs, as digitalis, morphine, calcium chloride and chloroform, increased the carotid sinus reflex response.

The results reported in this paper and in the previous ones substantiate the fact that the incidence and degree of response are greatly enhanced by arteriosclerotic heart disease, where the greatest degree of response is obtained. Other disease states, however, are associated with the reflex in greater or less incidence. Sex and age play a rôle in determining the response, being greater among males and in advancing age. Various types of disease likewise appear to have some influence. Patients with neuro-circulatory disturbances and no real organic disease appear to present the least incidence and degree of response. Hypertension, although increasing the incidence, decreases the degree of response. One interesting observa-

tion in this paper is that besides the greater male incidence of increase in the carotid sinus reflex, the reflex seems to occur in greater number and degree earlier in life among males than among females

All these factors point to a constitutional vagotonic tendency which is influenced by various factors. Disturbances in internal secretions undoubtedly play a part in influencing the reflex, as evidenced by the variations in the sex incidences of response, in the same disease states. The nervous state of the individual is another factor as evidenced by the diminished response in neurocirculatory asthenia. The gradual increase in response with advancing age may be due to a gradual and progressive sensitization of the vagal center by toxic states. The increase in the *incidence* of response in hypertension may be explainable on the basis of sensitization of the receptor nerve endings in the carotid sinus by increased intra-carotid pressure. This also partly explains the diminished response in neurocirculatory asthenia where the blood pressure is usually low. The persistent stimulation in hypertension appears to induce a moderate fatigue of the receptors, diminishing the *degree* of response.

SUMMARY

In previous reports an analysis was made of the slowing of the heart induced by the carotid sinus reflex, in a series of 345 cases. This paper deals with a similar analysis of 426 additional cases. This series was divided into seven groups: (1) arteriosclerotic heart disease, (2) hypertension and hypertensive heart disease, (3) arteriosclerotic and hypertensive heart disease, (4) rheumatic heart disease, (5) psychoneurotic heart disease, (6) other forms of heart disease or disturbances, and (7) general constitutional disturbances (non-cardiac).

It was found that the greatest frequency and degree of slowing occur in arteriosclerotic and hypertensive heart disease. Rheumatic heart disease comes next and general constitutional disease follows. The psychoneurotic and the miscellaneous groups of heart disease showed the least response. Hypertension seems to increase the frequency but to diminish the degree of the carotid sinus reflex response. The incidence and degree of response are greater among males than females and increase with advancing age. Males show the response in greater degree and incidence earlier in life than females.

The cardio-inhibitory reflex appears to depend on a constitutional vagotonic tendency which is more marked among males and develops with advancing age. General toxic or irritative states, endocrine factors, intra-carotid blood pressure, and local disease or disturbances in the heart itself, seem to play a part in sensitizing the reflex.

REFERENCES

- 1 SIGLER, L H Clinical observations on the carotid sinus reflex I The frequency and the degree of response to carotid sinus pressure under various disease states, *Am Jr Med Sci*, 1933, clxxxvi, 118
- 2 SIGLER, L H Clinical observations on the carotid sinus reflex II The response to carotid sinus pressure at various ages and heart rates and rhythms, *Am Jr Med Sci*, 1933, clxxxvi, 118
- 3 SIGLER, L H Clinical observations on the carotid sinus reflex III The response to carotid sinus pressure in cases with and without precordial pain, *Am Jr Med Sci*, 1933, clxxxvi, 125
- 4 SIGLER, L H Electrocardiographic observations on the carotid sinus reflex, *Am Heart Jr*, 1934, ix, 782
- 5 HEYMANS, C Le sinus carotidien et les autres zone vasosensibles reflexogenes, 1929, H K Lewis and Co, London
- 6 HERING, H E Karotissinusreflexe auf Herz und Gefasse, 1927, Dresden and Leipzig, Verlag Theodor Steinkopff
- 7 KOCH, E Über dem depressorischen Gefassreflex beim Karotisdruckersuch an Menschen, *Munchen med Wchnschr*, 1924, lxxi, 704
- 8 RAGINERS, P Le sinus carotidien du clinique, *Rev Belge Soc Med*, 1930, ii, 601
- 9 BRONK, D W, FERGUSON, L K, and SOLANDT, D Y Inhibition of cardiac accelerator impulse by way of the carotid sinus, *Proc Soc Exper Biol and Med*, 1934, xxxi, 579
- 10 SANDER, A C U S Vet Bur Med Bull, 1923, vii, 212
- 11 KEELE, C A Pathological changes in carotid sinus and their relation to hypertension, *Quart Jr Med*, 1933, ii, 213-220
- 12 BRAUN, L, and SAMET, B "Vagusdruck" und Koronargefass, *Deutsch Arch f klin Med*, 1928, clxi, 257-270
- 13 DANIELOPOLU, D, and MISSIRLIN, V Excitabilite centrifuge du vague dans les hypertones generales et les lesions chroniques, *Compt rend Soc de biol*, 1925, xcii, 538-540
- 14 WENCKEBACH, K F, and WINTERBERG, H Die unregelmassige Herztaetigkeit, 1927, Wilhelm Engelmann, Leipzig, p 128

PHOSPHATASE CONTENT OF HUMAN SERUM IN PULMONARY TUBERCULOSIS FOLLOWING THE ADMINISTRATION OF VITAMIN D *

By PAUL D. CRIMM, A. B., M. D., F. A. C. S., and J. W. STRAYER, A. B., M. D.,
Evansville, Indiana

PHOSPHATASE is an organic catalyst capable of either synthesizing or hydrolyzing any mono-ester of phosphoric acid. It was first discovered in rice and wheat bran by Suzuki, Yoshimura and Takaishi¹ in 1907. (For a full review of the literature see Kay²) It is present in large quantities in the intestinal mucosa, kidney and bone. Smaller quantities are found in practically all other organs and secretions. Fetal bone and the bone of young animals are richest in the enzyme, but the content diminishes as maturity is reached. The optimum pH in vitro is around 9—it is activated by Mg (Erdtman³) and inhibited by pepsin, iso-leucine and glycine (Bakwin and O. Bodansky⁴). Robison and Soames⁵ have shown its importance as a local factor in bone formation and have demonstrated the precipitation of calcium phosphate in bone slices, from a rachitic animal, immersed in calcium glycerophosphate. We have recently shown,⁶ supporting the work of other investigators,^{7, 8} that in the rat the phosphatase content of serum and kidney is reduced following massive doses of viosterol and that it is greatly increased in the small intestine. Changes in the bone were found to be variable.

METHOD

Determinations of serum phosphatase were made upon normal human beings and upon tuberculous individuals before and after the administration of viosterol, according to the method of Bodansky^{9, 10}. Blood samples were obtained in each case within an hour after the noon meal. The blood was centrifuged and all determinations were made immediately. The unit of phosphatase is equivalent to 1 mg. of phosphorus liberated from a glycerophosphate substrate in one hour at pH 8.6 and at 37° C. The calcium determinations were made simultaneously from the same specimen of serum.

EXPERIMENTAL

Blood Serum Phosphatase in Normal Humans Serum phosphatase determinations were made on 19 normal human beings (table 1). The lowest figure was 1.68 units and the highest 4.96 units per 100 c.c., the average being 3.31 units. In one case, not recorded in the table, the serum phosphorus and substrate phosphorus were respectively 4.49 and 14.14,

* Received for publication November 13, 1935.

From the Research Laboratory, Boelene Tuberculosis Hospital.

yielding 9.65 units of phosphatase. There was no apparent reason for this. Bakwin and Bodansky¹ give the normal range as being between 1.5 and 4.5 units per 100 c c.

TABLE I
Serum Phosphatase of Normal Human Beings

Case Number	Serum Phosphorus Mg per 100 c c	Substrate Phosphorus Mg per 100 c c	Units Phosphatase (By Difference)
1	3.40	6.82	3.42
2	4.21	5.89	1.68
3	3.53	8.27	4.74
4	3.46	6.47	3.01
5	3.42	7.48	4.06
6	3.78	7.92	3.14
7	2.48	5.32	2.84
8	3.95	7.35	3.40
9	3.57	8.53	4.96
10	3.80	7.57	3.77
11	2.58	6.47	3.89
12	3.82	6.42	2.60
13	3.95	6.95	3.00
14	3.10	6.73	3.63
15	3.57	5.66	2.09
16	3.42	5.94	2.52
17	3.38	5.33	1.95
18	3.27	6.29	3.02
19	2.48	6.73	4.25
Average	3.43	6.74	3.31

Blood Serum Phosphatase in Pulmonary Tuberculosis The phosphatase of the serum of 32 cases of pulmonary tuberculosis ranged from 1.36 to 4.45 units, with exception of one case which was 6.38 units (table 2). In three additional cases, all of which were moribund, the phosphatase content averaged 12.06 units per 100 c c (table 3).

In any stage of pulmonary tuberculosis the phosphatase activity is not greatly disturbed, and the values fall within normal limits. The reason for the elevation in the moribund cases is not known. The three cases mentioned above were in an extreme state of emaciation and cachexia. It is not to be inferred, however, that an elevated phosphatase content is a sign of impending death, since other patients in this series have since died, and bloods obtained post mortem on still others were quite normal for phosphatase.

Blood Serum Phosphatase in Tuberculous Patients Following Administration of Vitamin D Twenty-four tuberculous patients were given viosterol, 10,000 X,* 1 c c daily for 10 days. The calcium, phosphorus and phosphatase content of the sera was determined before and after administration. No attempt was made to secure a great elevation of serum calcium. If the patients became toxic before taking the full dosage of 10 c c the drug was discontinued. The average serum calcium before the administration

* 10,000 times average cod liver oil, 1,000,000 I U per gram, kindly supplied by Mead Johnson and Company, Evansville, Indiana.

TABLE II
Serum Phosphatase in Pulmonary Tuberculosis

Case Number	Serum Phosphorus Mg per 100 c c	Substrate Phosphorus Mg per 100 c c	Units Phosphatase (Bv Difference)
1	3.94	7.57	3.63
2	3.99	8.44	4.45
3	2.60	6.29	3.69
4	3.19	6.20	3.01
5	2.70	6.68	3.98
6	3.23	6.41	3.18
7	3.31	7.39	4.08
8	2.77	6.11	3.34
9	2.77	4.79	2.02
10	2.37	4.18	1.81
11	3.80	5.95	2.15
12	3.14	4.53	1.39
13	3.02	6.33	3.21
14	2.85	5.10	2.25
15	3.29	5.67	2.38
16	2.56	4.66	2.10
17	3.86	7.08	3.22
18	3.78	10.16	6.38
19	2.36	5.98	3.62
20	3.08	6.16	3.08
21	2.81	5.76	2.95
22	3.50	6.51	3.01
23	3.43	5.32	1.89
24	3.43	5.12	1.69
25	3.48	5.94	2.46
26	3.27	5.63	1.36
27	3.65	6.44	2.79
28	3.27	7.34	4.07
29	3.88	7.26	3.38
30	2.94	5.01	2.07
31	3.02	5.40	2.38
32	3.63	6.55	2.92
Average	3.22	6.17	2.95

TABLE III
Serum Phosphatase in Three Moribund Cases of Pulmonary Tuberculosis

Case Number	Serum Phosphorus Mg per 100 c c	Substrate Phosphorus Mg per 100 c c	Units Phosphatase (Bv Difference)
1	4.26	17.74	13.48
2	3.60	15.40	11.80
3	4.11	15.00	10.89
Average	3.99	16.05	12.06

of viosterol was 11.8 mg per 100 c c of blood serum. Following administration of viosterol 24 blood sera averaged 14.2 mg per 100 c c. In the same patients the phosphatase content of the blood serum before administration of viosterol averaged 3.29 units per 100 c c and 3.06 units per 100 c c following administration of viosterol. This shows a slight decrease in

TABLE IV

Twenty-Four Cases of Pulmonary Tuberculosis before and after the Administration of Viosterol, 10,000 X

Case Number	Serum Calcium (Mg per 100 c c of Blood Serum)		Serum Phosphatase Units per 100 c c of Blood Serum	
	Before Viosterol	After Viosterol	Before Viosterol	After Viosterol
1	11.5	12.5	2.45	2.26
2	11.7	11.3	3.03	3.73
3	11.5	13.0	4.38	4.43
4	11.6	12.5	4.52	4.41
5	11.5	13.3	3.11	2.95
6	12.0	12.9	2.53	1.79
7	11.1	15.2	3.76	3.04
8	12.1	16.4	3.99	5.16
9	11.0	13.5	2.63	2.85
10	11.8	18.6	2.66	2.39
11	10.5	14.4	3.96	4.39
12	11.8	17.2	3.06	2.02
13	12.8	15.6	4.36	2.74
14	12.1	15.6	3.23	1.26
15	10.8	13.8	2.64	3.13
16	9.9	14.3	2.97	3.09
17	10.8	13.3	3.90	3.47
18	12.2	13.1	2.23	3.92
19	12.7	14.4	3.04	3.00
20	13.0	13.3	2.57	2.64
21	12.9	13.3	2.62	2.24
22	12.6	16.3	3.53	1.64
23	12.7	13.5	4.61	3.45
24	12.4	14.2	3.33	3.43
Average	11.8	14.2	3.29	3.06

the phosphatase content. A detailed analysis shows that a decrease of phosphatase occurred in 14 cases, whereas in 10 there was an increase of phosphatase in the blood serum. However, in 11 patients who had an elevation of the serum calcium over 14.0 mg per 100 c c, seven showed a decrease in the phosphatase content, while four showed an increase.

SUMMARY

1. The phosphatase content of a normal human serum was found to average 3.31 units in a series of 19 cases.

2. In 32 cases of pulmonary tuberculosis, all stages, the phosphatase content averaged 2.95 units.

3. Administration of viosterol, 10,000 X, in dosage resulting in hypercalcemia, caused a slight reduction of serum phosphatase in blood serum. Fourteen cases of pulmonary tuberculosis showed a decrease while ten showed an increase. Seven of the 11 whose serum calcium was 14.0 mg or over showed a decrease in serum phosphatase content.

BIBLIOGRAPHY

- 1 SUZUKI, U, YOSHIMURA, K, and TAKAISHI, M Über ein Enzym "Phytase" das "Anhydro- α -methyl-en-diphosphorsäure" spaltet, Bull Coll of Agric, Tokyo, 1907, vii, 503
- 2 KAY, H D Phosphatase in growth and disease of bone, *Physiol Rev*, 1932, xi, 384-422
- 3 ERDTMAN, H Glycerophosphatspaltung durch Nierenphosphatase und ihre Aktivierung, *Ztschr f Physiol Chem*, 1927, cxxvii, 182-198
- 4 BAKWIN, H, and BODANSKY, O Factors influencing measurement of the phosphatase activity of tissue extract, *Jr Biol Chem*, 1933, ci, 641-656
- 5 ROBISON, R, and SOAMES, K M The possible significance of hexosephosphoric esters in ossification VIII Calcification in vitro, *Biochem Jr*, 1930, xxiv, 1922-1926
- 6 CRIMM, P D, and STRAYER, J W Phosphatase content of blood serum and tissues in the rat following administration of vitamins D and A, *Jr Biol Chem*, 1936, cxii, 511-515
- 7 TAYLOR, N B, WILD, C B, BRANTON, H D, and KAY, H D A study of the action of irradiated ergosterol and of its relationship to parathyroid function, Part I, *Canad Med Assoc Jr*, 1931, xxiv, 763-777
- 8 TAYLOR, N C, WILD, C B, BRANTON, H D, and KAY, H D A study of the action of irradiated ergosterol and of its relationship to parathyroid function, Part II, *Canad Med Assoc Jr*, 1931, xxv, 20-35
- 9 BODANSKY, A Phosphatase studies II Determination of serum phosphatase Factors influencing the accuracy of the determination, *Jr Biol Chem*, 1933, ci, 93-104
- 10 BODANSKY, A Phosphatase studies I Determination of inorganic phosphate Beer's law and interfering substances in the Kuttner, Lichtenstein method, *Jr Biol Chem*, 1932, xcix, 197-206

DIAGNOSIS OF DISSECTING ANEURYSM OF THE AORTA¹

By EDWIN E. OSGOOD, M.D., M. F. GOURLEY, M.D., and RUSSEL L. BAKER, M.D., *Portland, Oregon*

ALTHOUGH more than 400 cases of dissecting aneurysm have been reported, only 11 have been correctly diagnosed during life. Shennan,¹ in an extensive review of the literature up to 1933, accepts six cases. He does not accept the cases of Finny (1885), Prescott (1897), Mager (1908), and Heller (1904). Since Shennan's review, five more cases² have been diagnosed during life. Hamman⁴ and Gatewood⁵ have each diagnosed a case after death but before the necropsy findings were known.

The purpose of this paper is to report two additional cases diagnosed during life and to outline briefly the clinical and pathologic features of this condition. It is hoped that our summary of the salient characteristics of dissecting aortic aneurysm will result in its more frequent recognition during life.

CASE REPORTS

Case 1. J. N. S., a white male, aged 50, entered Multnomah County Hospital on Oct. 18, 1934, complaining of pain in the abdomen and chest, with vomiting. The patient was well until 2:30 p.m., of the day of entrance when, following a heavy meal, he was suddenly seized with a steady, sharp pain in the epigastrium and lower chest, radiating to the right and left sides of the abdomen, to the back of the chest and into the left flank. The pain was diffuse and poorly localized. Lying flat on the floor was the only position which afforded relief. There was no vomiting at this time but definite nausea. After a short time the pain gradually subsided but soon recurred with greater intensity and remained steady with no cramp-like exacerbations. There was some shortness of breath associated with the pain, and the patient felt as though his heart was "about to jump out of his body." There was also some dizziness and spots before the eyes. Vomiting first occurred at 7:00 p.m. and was repeated six times in the next four hours.

From the past history it was learned that the patient contracted syphilis about 1917 but was treated for only a short time. In August 1932, he entered Multnomah County Hospital where a diagnosis of syphilitic meningitis and hypertensive cardiovascular renal disease was made. The Kolmer and Kahn were 4 plus. Following his discharge he was treated in the Outpatient Syphilis Clinic. In September 1933, he reentered the hospital with a diagnosis of basilar subarachnoid hemorrhage on the basis of hypertensive disease or syphilitic vascular changes. The blood pressure at this time was 190 systolic and 118 diastolic. He was discharged Dec. 10, 1933 and was in fairly good health until the onset of the present illness.

Physical examination on Oct. 19, 1934 revealed a well developed, well nourished, middle-aged male, obviously in pain, preferring to lie on his right side but occasionally turning from side to side and very apprehensive. His face was flushed but not cyanotic. There was no dyspnea. The blood pressure was 182 systolic and 88 diastolic and equal in both arms. The pulse was 98 and regular, the temperature,

* Received for publication November 19, 1935.

From the Department of Medicine, University of Oregon Medical School and Multnomah County Hospital, Portland, Oregon.

100° F (37.8° C) Vigorous systolic pulsation was visible in the carotid vessels and palpable in the suprasternal notch and over the left subclavian artery. The peripheral vessels were tortuous and thickened with some sclerotic beading. The heart was enlarged, particularly to the left, and the pulsations were strong. The impact of the aortic valve closure was palpable. Percussion showed upper sternal dullness of considerable degree. The heart was aortic in configuration with widening of the base. The heart tones were clear and sharp, and there was a long blowing systolic murmur over the mitral area. The aortic second sound was markedly accentuated but not metallic in character. There was no murmur over the aorta posteriorly. The lungs showed no evidence of congestion. There was moderate resistance over the upper abdomen particularly on the left side, but no definite area of localized tenderness. Excursion of the costal margin with deep inspiration was normal. There were no changes in the extremities, the peripheral vessels showed equal normal pulsation.

The diagnosis on admission was coronary thrombosis or some form of acute abdominal disease. Because of the presence of long standing hypertension on the basis of hypertensive cardiovascular renal disease, the diffuse nature of the pain, radiating to the back, the maintenance of good heart tones and high systolic blood pressure, the absence of evidence of congestive failure and of clear cut evidence of intra-abdominal pathology, a diagnosis of dissecting aneurysm of the aorta was made by the staff physician (M. F. G.).

Laboratory examination showed 2 plus albumin and 4 plus acetone and diacetic acid in the urine. The blood examination revealed 14.3 gm (103.3 per cent) of hemoglobin (Osgood-Haskins), 4.09 million red cells, 9,900 white cells, with a normal differential count. The sedimentation rate by the modified Westergren method⁶ was 12 mm in 15 minutes and 20 mm in 45 minutes, increasing to 45 mm in 15 minutes and 97 mm in 45 minutes by the fifth day. The blood urea nitrogen was 14.50 mg per 100 cc of blood. The icterus index was 7. The Kolmer and Kahn were negative at this time.

A roentgenogram (figure 1) of the chest showed deviation of the upper mediastinum to the right and an enlarged heart of aortic configuration with evidence of an aneurysm of the descending limb of the aorta.

The electrocardiogram (figure 2) showed left axis deviation, regular sinus rhythm, an inverted T-wave in Leads I and II, and a depressed S-T interval in Lead I.

For the first few days the patient had a slight fever. The pain remained about the same in character but was relieved by morphine sulphate, 10 mg every four hours, a little later paraldehyde, 8 cc, once or twice in 24 hours, controlled the pain. The pain and temperature gradually decreased and the patient was discharged Dec 16, 1934, 59 days after entrance.

He reentered the hospital Feb 16, 1935, complaining of shortness of breath, swelling of the ankles, chest pain, headache, dizziness, spots before the eyes, palpitation of the heart, and weakness. Since his discharge the previous December, the pain, though much diminished, had persisted, and there was some shortness of breath and swelling of the ankles associated with nocturia of three to four times. This condition persisted until Feb 16, 1935 when he was again incapacitated by the increase in lower chest pain and shortness of breath. The dyspnea was so severe that he was forced to sit up in bed. The pain at times radiated through to the back and down the inside of the right arm.

Physical examination showed extreme orthopnea, flushed face, nervousness, and marked pulsation of the carotid vessels. The blood pressure was 135 systolic and 110 diastolic, the respirations were 30, the pulse, 100 and regular, the temperature, 99° F (37.3° C). The chest showed bilateral basal moisture. The cardiac findings were the same as at the previous examination. The trachea was slightly deviated to the

right There was some engorgement of the systemic veins The liver was tender but not enlarged There was no edema of the ankles

The laboratory examination was essentially the same as on the previous entrance

An electrocardiogram (figure 3), Feb 18, 1935, showed a regular sinus rhythm, a left axis deviation, a depression of the S-T interval in Leads I and II and a high



FIG 1 Roentgenogram of the heart in Case 1, taken Oct 18, 1934 Note the aneurysmal dilatation of the descending aortic arch, the aortic configuration of the heart and the deviation of the trachea to the right

take-off in Lead III, and a diphasic T-wave in Lead I These findings were strongly suggestive of a recent coronary thrombosis and differed decidedly from the previous tracing

The patient expired suddenly five days after admission

Necropsy revealed pericardial tamponade due to hemorrhage from intrapericardial perforation of a recent dissecting aneurysm confined to the ascending aorta. In addition, an old dissecting aneurysm extending from the arch of the aorta into the common iliac arteries was found. The walls of this aneurysm were completely re-endothelialized. The heart weighed 650 gm. Serial sections of the coronary arteries

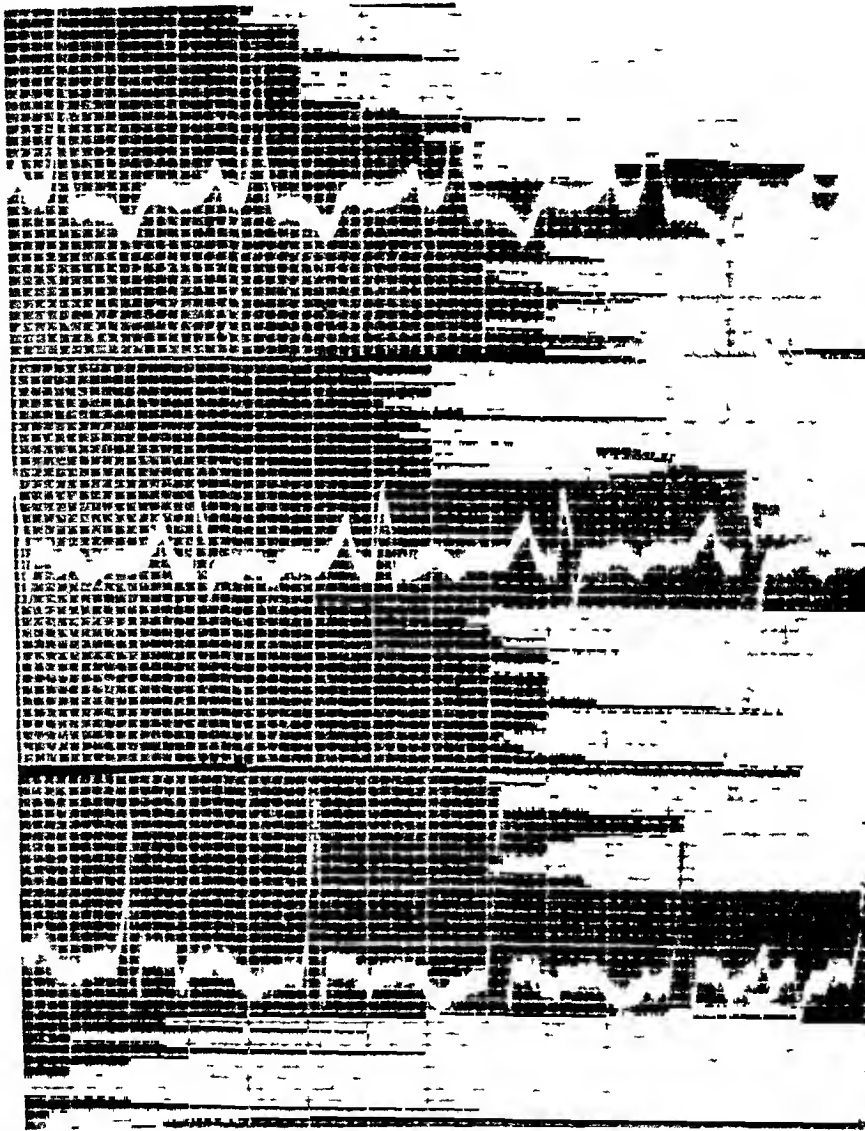


FIG 2 Electrocardiogram in Case 1, taken Oct 26, 1934. Note the negative T-waves in Leads I and II and the evidence of left axis deviation.

showed numerous atherosclerotic plaques but the lumens were widely patent. The myocardium showed no fibrosis. The final anatomic diagnosis was perforation of dissecting aortic aneurysm with hemorrhage into the pericardial sac, dissecting aneurysm of the aorta and common iliac arteries, and syphilitic aortitis.

Case 2 R A Y, a huge white man, aged 43, entered Multnomah County Hospital at 3 30 p m, Jan 28, 1935, complaining of severe tearing pain in the chest, ab-

domen, and back. He had felt well until Dec 25, 1934, when, following a heavy Christmas dinner, he called a physician for an attack of "indigestion." The physician told him he had high blood pressure and that he had had a heart attack. A second similar attack occurred Jan 5, 1935, following which he returned to his work as a boiler fireman. He was awakened at 11 00 p m Jan 27, 1935 by a mild pain in the chest which at 1 00 a m became suddenly very severe and tearing in character as if

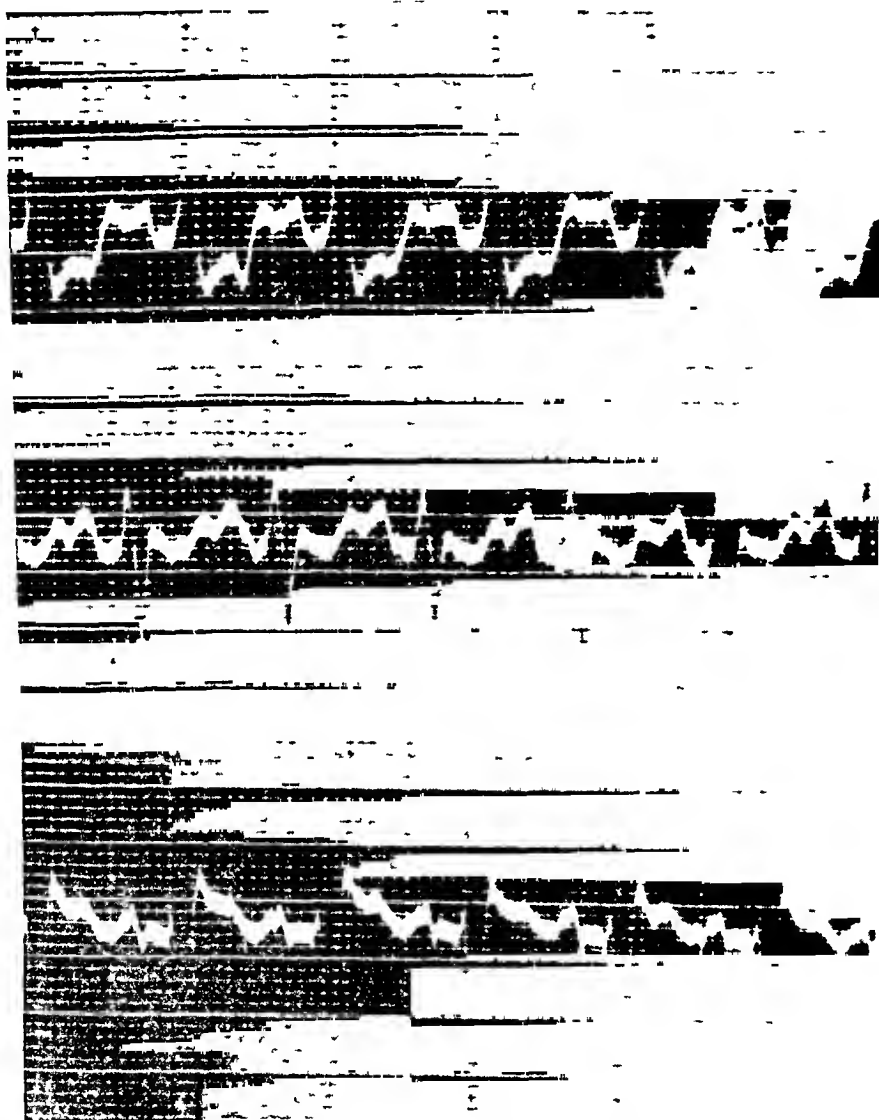


FIG 3 Electrocardiogram of Case 1, taken Feb 18, 1935. Note the marked change from the previous electrocardiogram and the evidences of coronary occlusion, although none was found at necropsy.

"something had broken" in his chest. The site of maximum intensity of the pain changed from the front of the chest to the left shoulder and then to the abdomen and the lumbar region. The pain became excruciating and he vomited once at 4 00 a m. The pain had continued unabated, notwithstanding two hypodermic injections, presumably of morphine.

Physical examination revealed a powerfully built man weighing 297 pounds, obviously in severe pain. The temperature was 99.2°F (37.3°C), the pulse, 93, and respirations, 20 per minute. The blood pressure was 260 systolic and 145 diastolic. The fundi showed notching of the veins and narrowing of the arteries. A vigorous carotid pulsation was noted on the right side of the neck. The heart was markedly enlarged, of aortic configuration with a forceful apex beat, regular rhythm,

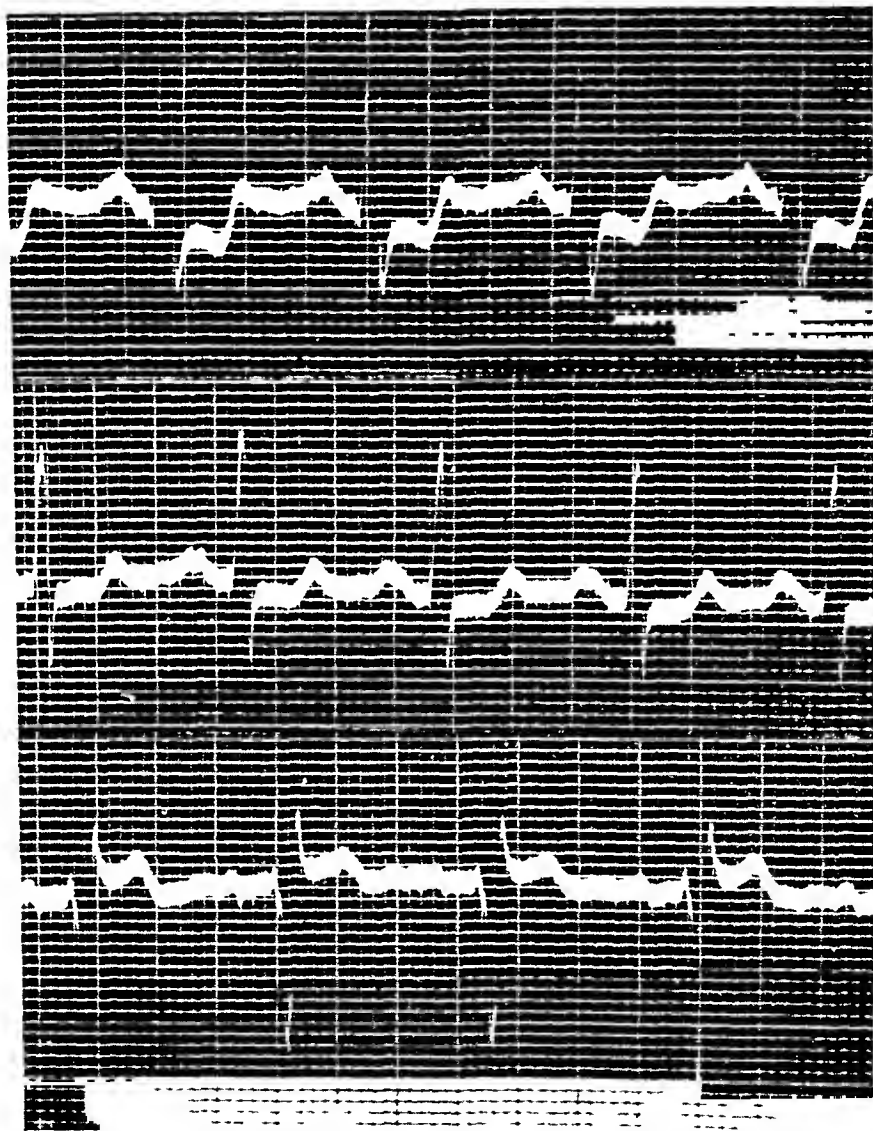


FIG 4 Electrocardiogram of Case 2, taken Feb 4, 1935. Note the diphasic T-waves in Leads I and II, the depressed S-T interval in Lead I and the elevated S-T interval in Lead III as well as the left axis deviation.

a loud booming aortic second sound, but no murmurs. The peripheral vessels showed 2 plus thickening of the "rubber tube" type characteristic of hypertensive cardiovascular renal disease.

Laboratory studies revealed a 2 plus albuminuria with hyaline casts, normal red cell count and hemoglobin, an icterus index of 18, a white cell count of 10,000 with 67

per cent segmented neutrophils and 3 per cent staff cells. The sedimentation rate⁶ was 55 mm in 15 minutes and 85 mm in 45 minutes. The blood urea nitrogen was 17 mg per 100 cc of blood. The Kolmer and Kahn tests were negative.

The electrocardiogram (figure 4) showed a regular sinus rhythm with a rate of 88, a P-R interval of 0.18 second, a diphasic T₁, a depressed S-T interval in Lead I, a high S-T interval in Lead III, and left axis deviation.



FIG 5 Roentgenogram of Case 2, taken Feb 11, 1935. Note the aneurysmal dilatation of the aorta and the deviation of the trachea to the right.

A six foot roentgenogram (figure 5) of the chest revealed passive congestion at the bases of both lungs, a greatly enlarged heart of aortic configuration with a widened, distorted aorta shadow of increased density displacing the trachea to the right but showing no sacular dilatation.

The pain in the chest and back persisted until his death, February 17. It was not affected by a test dose of nitroglycerine and was only partially relieved by 15 to 30 mg of morphine sulphate administered every three to four hours until death. February 12, a systolic murmur was noted over the dorsal and lumbar spines with

the point of maximum intensity at the level of the tenth dorsal spine. The blood pressure maintained a level of about 240 systolic and 140 diastolic. The pulse rate varied between 80 and 100 and the temperature between 97.0° F (36.1° C) and 100.0° F (37.8° C). At 2.30 a.m., February 17, the patient was sleeping when seen by the nurse. At 3.30 a.m., he was found dead in bed.

A clinical diagnosis of hypertensive cardiovascular renal disease with acute coronary thrombosis was made on admission by the intern (R. L. B.). The tearing quality of the pain and its radiation to the back with no signs of congestive failure and no fall in blood pressure suggested the diagnosis of dissecting aneurysm of the aorta to the staff physician (E. E. O.). This diagnosis was confirmed by discovery of the murmur radiating down the spine, by the findings in the roentgenogram, and by the icterus index. The final clinical diagnosis was dissecting aneurysm of the thoracic and abdominal aorta with terminal rupture, hypertensive cardiovascular renal disease with left ventricular hypertrophy, regular sinus rhythm, and familial obesity.

Necropsy revealed hypertrophy and dilatation of the left ventricle and a dissecting aneurysm extending from the level of the attachment of the ductus arteriosus to the bifurcation of the aorta, with a perforation just beyond the arch into the left pleural cavity into which a massive hemorrhage had occurred. Microscopically, sections of the aorta revealed many small scars in the media with lymphocytic infiltration about the vasa vasorum. An organized blood clot was attached to one side of the split media. The intima was thickened and diffusely infiltrated with lymphocytes and plasma cells.

DISCUSSION

Dissecting aneurysm, or aneurysm dissecans, of the aorta is characterized, clinically, by the sudden onset in a patient with hypertension, of severe, tearing pain in the chest, usually radiating to the back, followed, after a variable interval, by sudden death, and is characterized, pathologically, by a primary rupture of the intima with a splitting of the media, and a secondary rupture externally or, less commonly, back into the lumen.

Etiology. The exciting cause in nearly all cases is hypertension. The cause of the hypertension is usually hypertensive cardiovascular renal disease, less commonly nephritis. Thirteen cases have been reported in patients with coarctation of the aorta and one⁷ in a patient with basophilic adenoma of the pituitary. The usual predisposing cause is a sudden rise in blood pressure due to excitement, exertion, trauma, distention of the stomach, or vomiting. A history of static strain as in wrestling, lifting, or straining at stool is especially common. The age distribution is that of the diseases causing the hypertension. The youngest cases are those with coarctation of the aorta or nephritis. The majority occur between the ages of 40 and 70 when hypertensive cardiovascular renal disease has its greatest incidence. The condition is more common in males (65 per cent) than in females probably because of the greater exposure to unusual strain.

The rôle of syphilitic aortitis is controversial. Loeschke,⁸ 1928, believed that syphilis had a tendency to bind the aortic wall, thus preventing wide dissections. Kellogg and Heald,^{3b} 1933, stated "It seems probable that the lesions of syphilis in the aorta, being more focal in their intensity, lead to a localized rather than a generalized weakening of the wall."

Samson,¹⁰ 1931, said "It seems probable that a luctic meso-aortitis, through an interference with the blood supply leads to a degeneration of the medial fibers, and a somewhat displaced arrangement, saccular aneurysm being the sequel instead of the dissecting type" Shennan,¹ 1934, feels that syphilis may play a dual rôle in the production of dissecting aneurysm. In some cases it seems that the process is not sufficiently established to resist the splitting of the laminae, and in others, a toxic necrosis of the muscularis, in the absence of infiltration and adventitial changes, so weakens the aortic wall as to allow wide dissection. The association of the two conditions seems to us to be merely a coincidence. We do not believe syphilitic aortitis either predisposes to, or prevents, dissecting aneurysm. The incidence of syphilis (10 per cent) in patients with dissecting aneurysm is not materially greater than the incidence of syphilis in the general population of this age and sex group. The site of rupture is usually in an area of medial degeneration of the type occurring in hypertensive cardiovascular renal disease rather than at the site of a syphilitic lesion. Syphilis is certainly not an important predisposing factor because the great majority of the patients had no clinical or pathologic evidence of this disease, and in the cases which were associated with syphilitic aortitis there was usually coexistent hypertension or otherwise unexplained left ventricular hypertrophy.

Pathology The pathology has recently been thoroughly discussed by Shennan¹ and most of the statements that follow are summarized from his data. Dissecting aneurysm is noted once in every 300 to 500 necropsies.^{3c} The essential pathology is a rupture of the intima with a splitting of the media. In most instances there is a secondary rupture externally and, in a few cases, secondary rupture back into the lumen of the aorta.

In about 70 per cent of the cases the initial rupture is in the ascending aorta, in about 20 per cent in the transverse arch, and in about 10 per cent in the descending thoracic or abdominal aorta. The length of the dissection varies from a few centimeters to the entire length of the aorta and occasionally extends as far down as the popliteal arteries. In about 30 per cent of the cases the dissection is confined to the ascending or transverse arch, and in about 35 per cent the abdominal aorta is involved. Usually the major dissection is in a distal direction, but in about 10 per cent of cases it is in a proximal direction.

In about 95 per cent of cases, death is due to secondary rupture of the aorta. Seventy per cent of cases rupture into the pericardial sac, 20 per cent into the left pleural cavity, 5 per cent into the mediastinum, and a few cases into the right pleural cavity, the abdominal cavity or the retroperitoneal tissues. One reported case ruptured into the pulmonary artery.

The most constant associated pathology is left ventricular hypertrophy, present in about 85 per cent of the cases reported. Some degree of medial degeneration is usually demonstrable. Syphilitic aortitis is associated in about 10 per cent of all cases. Atheromatous changes are present in about

50 per cent of the cases, as might be expected from the age distribution, but the atheromatous lesions show little relation to the dissection

Shennan² discusses the various theories of pathogenesis and concludes that medial degeneration is the most important factor. From the analysis of his data and the other reported cases, it seems to the authors that hypertension is by far the most important factor in the pathogenesis.

Clinical Characteristics The patient is usually first seen just after the sudden onset of severe pain in the chest and back. Questioning may elicit a familial history of a "stroke" or high blood pressure, and a past history of high blood pressure, nocturnal polyuria, or occipital headaches suggestive of hypertensive cardiovascular renal disease. In younger patients there may be a history characteristic of preexisting nephritis or coarctation of the aorta. The pain usually begins following excitement, exertion, or injury. It is described as sharp, tearing, or as if something had broken in the chest. Its point of maximum intensity is usually over the middle or upper sternum and its most common radiation is into the region of the mid-dorsal spine. It may radiate to the abdomen, lumbar region, shoulder blades, neck, or down the arm. Its segmental distribution is likely to be higher than that of coronary artery disease.¹⁰ It is often diffuse, localized with difficulty, and is usually very severe, requiring large doses of morphine to control it. It is associated with extreme restlessness and persists unabated for many days. There is a tendency to sudden exacerbations in intensity with migration of the points of reference, indicating the development of further dissections. Dysphagia is sometimes present.

Physical examination reveals an apprehensive individual, obviously in severe pain. Cyanosis and dyspnea are often present. Fever of slight degree is common. The increased rate of pulse and respiration is probably secondary to the severe pain. The blood vessels show the "rubber tube" type of thickening, characteristic of hypertensive cardiovascular renal disease. Unless in shock, the blood pressure is high. It may be lower in the left arm or in the lower extremities than in the right arm. Absence of the pulse in the left arm, carotids, or inferior extremities has been recorded. The trachea may be deviated to the right. Percussion of the heart reveals an aortic configuration with dullness under the upper sternum. Signs of congestive failure are usually absent. The aortic second sound is typically accentuated but murmurs over the heart are not characteristic. Auscultation over the dorsal and lumbar spines, the abdominal aorta, or the femoral arteries may reveal a systolic murmur transmitted downward. This may develop late in the course of the disease, so should be looked for daily. Coarctation of the aorta may produce a similar murmur but may be recognized by finding its characteristic collateral circulation. Signs of obstruction of any branch of the aorta may be present. Among these signs are coma, hemiplegia, anuria, gangrene of the extremities, paralytic ileus, or localized swellings over the chest, neck, or abdomen.

Sudden death supervenes within a few minutes in 65 per cent of the cases, a few days in 10 per cent of the cases, and after an interval of weeks to months in the majority of the remainder, although a few cases have been known to live for years. Death is due to rupture of the aorta, usually into the pericardium, less commonly into the pleural cavity, mediastinum, or abdomen. While only of academic interest, the site of rupture may be determinable after death by percussion of the absolute cardiac dullness, the lung fields, and the abdomen.

The most valuable laboratory change, when present, is an increase in the icterus index due to bilirubin formation from hemoglobin destruction in the clotted blood. Urobilinogen may be increased in the urine but bile pigment does not appear. Clinical jaundice is usually absent but occasionally slow hemorrhage may occur into the mediastinum or retroperitoneal tissues of sufficient extent to produce it as well as an anemia. A moderate neutrophilic leukocytosis is often present. Serologic tests for syphilis are usually negative but a positive test does not exclude this diagnosis. Renal function may be decreased or normal as in any patient with hypertension and should be determined.

Röntgenographic features have been well summarized by Wood, Pendergrass and Ostrum.⁹ These features consist of a diffuse widening along the shadow of the aortic arch with diminished pulsation, an enlarged heart of aortic configuration, displacement of the esophagus and trachea to the right, shadows of dissections along the branches of the aorta and evidences of fluid in the left pleural cavity.

The electrocardiogram shows nothing characteristic of this condition but frequently shows left axis deviation and evidences of myocardial damage from coronary disease as is common in any case of severe hypertension. If clear cut evidence of recent coronary thrombosis is absent the electrocardiogram is helpful, but evidence of coronary occlusion does not exclude dissecting aneurysm. The changes usually ascribed to coronary occlusion may occur in dissecting aneurysm when necropsy fails to reveal evidence of infarction as was true in our two cases.

Diagnosis. The diagnosis of dissecting aneurysm should not be difficult if this possibility is given adequate consideration. This diagnosis should be considered in any patient who develops sudden pain in the chest or who dies suddenly. Evidences of co-existing hypertensive disease, radiation of the pain to the back, migration of the pain, and the increase in the icterus index are the most helpful features. Evidences of congestive failure are usually absent. If, in addition, a systolic murmur over the dorsal and lumbar spines develops and coarctation of the aorta is excluded, the diagnosis becomes almost certain. The sequence of sudden chest pain followed by sudden death is in itself strongly suggestive of this condition.

Dissecting aneurysm must be differentiated from coronary occlusion, from syphilitic aneurysm, from pulmonary embolism, and from the other

causes of sudden death. The great majority of the reported cases of recent years were erroneously diagnosed as cases of coronary occlusion.

The differential diagnosis of coronary occlusion is not complete without a consideration of dissecting aneurysm. The chief points of differentiation are the radiation of pain to the back, the migration of pain, and the elevation of the icterus index in dissecting aneurysm, and in coronary occlusion the occurrence of pericarditis, and signs of myocardial degeneration such as a fall in blood pressure, congestive failure and typical electrocardiographic changes. Radiation of pain to the back is extremely rare in coronary occlusion and radiation to the lumbar or sacral regions is almost unknown. Pain in coronary occlusion is usually described as constricting or vise-like, that of dissecting aneurysm as tearing or as if something had broken. The elevation of the icterus index has not heretofore been described, but it is logical to expect that it would be present in most cases of dissecting aneurysm if studied between 12 hours and two weeks after the time of onset. The two conditions not infrequently coexist so that, contrary to some authors,³⁰ electrocardiographic evidence of coronary occlusion does not exclude dissecting aneurysm. Sudden death from rupture of the heart may follow a coronary occlusion.¹¹ These cases may be especially difficult to distinguish from cases of dissecting aneurysm with rupture into the pericardial sac.

Syphilitic aneurysm of the aorta is not necessarily associated with hypertension and rarely causes pain for the first time with the dramatic suddenness characteristic of dissecting aneurysm. It is usually preceded by a history of substernal oppression and syphilis, and is often associated with aortic regurgitation, or a ringing aortic second sound, or with laboratory or clinical evidence of syphilis. The greatest difficulty in differentiating syphilitic aneurysm from dissecting aneurysm will be encountered in those cases first seen after sudden death from rupture as both types of aneurysm may rupture into the same locations.

Pulmonary embolism may produce death with equally dramatic suddenness but occurs usually in patients who have been in bed for some length of time or who have chronic right sided cardiac dilatation.

Cases of traumatic dissecting aneurysm seen in shock might be confused with internal hemorrhage from a ruptured viscus but the arterial and cardiac evidences of preceding hypertension should be of help and the subsequent course decisive. All aneurysms secondary to trauma are of the dissecting type.

Coarctation of the aorta must be excluded in cases with a systolic murmur transmitted down the spine because it is the only condition other than dissecting aneurysm giving rise to this type of murmur. The collateral circulation in the back and roentgen evidence of erosions of the lower margins of the ribs characteristic of coarctation should be most helpful because both conditions may result in a lower blood pressure in the inferior extremities.

than in the upper. Coarctation of the aorta and dissecting aneurysm may coexist.

Prognosis The prognosis is very grave. Sixty-five per cent of the cases so far reported have died from perforation within a few minutes and 10 to 15 per cent more have died within a few days of the onset. Most of the remainder died within a few weeks or months but cases have been reported that have lived for many years. Most of these proved to be cases that have perforated into the lumen of the aorta.

Treatment The most important point in the treatment is absolute rest with avoidance of all types of strain which tend to raise the blood pressure. Education in methods of avoiding such strains in persons with an extremely high diastolic pressure may prevent the development of this condition. As soon as the condition is recognized, large doses of morphine should be given to allay the extreme pain and anxiety and should be repeated as necessary until the pain can be controlled by other medication, usually a matter of weeks. Special nursing care to relieve the patient of the necessity of making any exertion on his own behalf is desirable during the first week. Mineral oil and mild laxatives should be given to secure a soft enough bowel movement so that there is no necessity for straining. Bleeding and administration of nitrites would seem logical procedures if the blood pressure is markedly elevated. Just how long the period of rest should be continued is difficult to say but it certainly should be a matter of months after all pain has ceased, and the return to physical activity should be very gradual. The diet should be soft and adapted to the needs of the patient as regards calories and quality, taking into consideration the body weight and build, and the renal function. Symptomatic therapy should be given as indications arise.

SUMMARY AND CONCLUSIONS

Dissecting aneurysm should be diagnosed during life but only a few cases have been clinically recognized. Two cases diagnosed during life are reported. The essential features of the condition are summarized and the criteria which may aid in the recognition of this condition are given. If dissecting aneurysm of the aorta is considered whenever severe pain radiating to the back develops suddenly in a patient with hypertension and the case is analyzed by the methods here outlined, a correct diagnosis should usually be made. Careful analysis of the history is the most important single feature.

REFERENCES

- 1 SHENNAN, T. Dissecting aneurysms. Medical Research Council Monograph. Special Report Series, No. 193, London. Published by His Majesty's Stationery Office, 1934.
- 2 (a) SWAINF, K., and LATHAM, P. M. Case of dissecting aneurysm of the aorta, Trans. Path. Soc. London, 1855-56, vii, 106. (b) BAHRDT, R. Aneurysma dissecans der Bauchorta mit letalher Berstung zwischen die Mesocolonblätter des Colon descendens, Arch. d. Heilk., 1872, xiii, 473. (c) WISS, O. Aneurysma dissecans der Aorta ascendens, Arch. d. Heilk., 1869, v, 490. (d) DAVY, H., and GATES, M. Dissecting

- aneurysm of aorta, Brit Med Jr, 1922, i, 471-472 (c) MOOSBERGER, W Zur Symptomatologie des Aneurysma dissecans, Schweiz med Wchnschr, 1924, liv, 325 (f) BARTON, E M Dissecting aneurysm of aorta, Trans Chicago Path Soc, 1931, viii, 399-401
- 3 (a) SAMSON, P C Dissecting aneurysms of aorta, including traumatic type, three case reports, ANN INT MED, 1931, v, 117-130 (b) KELLOGG, F, and HEALD, A H Dissecting aneurysm of aorta report of case diagnosed during life, with pathologic study, Jr Am Med Assoc, 1933, c, 1157-1160 (c) WHITE, P D, BADGER, T L, and CASTLEMAN, B Dissecting aortic aneurysm wrongly diagnosed coronary thrombosis, Jr Am Med Assoc, 1934, ciii, 1135-1139 (Case diagnosed is mentioned in footnote) (d) LOUNSBURY, J B Clinical diagnosis of dissecting aneurysm of aorta, Yale Jr Biol and Med, 1935, vii, 209-214 (e) WEISS, S Clinical course of spontaneous dissecting aneurysm of aorta, Med Clin N Am, 1935, viii, 1117-1141
 - 4 HAMMAN, L, and APPERLY, F L Clinical pathological conference Instance of spontaneous rupture of aorta with aortic insufficiency, Internat Clin, 1933, iv, 251-272
 - 5 GATEWOOD, W E Personal communication
 - 6 OSGOOD, E E A textbook of laboratory diagnosis, 2 Ed, 1935, P Blakiston's Son and Co, Philadelphia, p 585
 - 7 LAWRENCE, J H, and ZIMMERMAN, H M Pituitary basophilism, report of case, Arch Int Med, 1935, lv, 745
 - 8 LOESCHKE, A Aneurysma dissecans auf luctischer Grundlage, Frankf Ztschr f Pathl, 1928, xxi, 56-81
 - 9 WOOD, F C, PENDERGRASS, E P, and OSTRUM, H W Dissecting aneurysm of aorta, with special reference to its roentgenographic features, Am Jr Roentgenol, 1932, xvi, 437-465
 - 10 GAGER, L T Symptoms of dissecting aneurysm of the aorta, ANN INT MED, 1929, ii, 658-664
 - 11 BENSON, R L, HUNTER, W C, and MANLOVE, C H Spontaneous rupture of heart, report of 40 cases in Portland, Oregon, Am Jr Path, 1933, ix, 295-328

DIET OF THE BLUFF DWELLERS OF THE OZARK MOUNTAINS AND ITS SKELETAL EFFECTS ⁴

By E G WAKEFIELD, M D, *Rochester, Minnesota*, and SAMUEL C DELLINGER, *Fayetteville, Arkansas*

IN another study we presented data on the diseases of bone which were prevalent among an ancient primitive race of people who inhabited the shelters of the bluffs in the Ozark Mountains of Arkansas and Missouri. The period of their occupation, from whence they came, or where they went are questions which cannot be answered. The absence of smooth stone or iron gadgets among their burial effects is mute evidence that they lived in ancient times and that they were very primitive people. Whether they lived twenty, thirty, or more centuries ago is irrelevant in this study.

In making a study of the osseous remains, the age of the bones is not as important as is the state of preservation. In the museum of the University of Arkansas there are four or five skeletons of children which are in a good state of preservation, and the isolated parts of many more. We believed that this number of bones of children of an extinct race, combined with a study of a great number of adult bones, would serve to indicate whether there was, at least, a tendency toward the development of deficiency diseases. In this material there also were several parts of bodies which were mummified. We were particularly interested in these mummified parts, in the hope that we could find some feces which we could examine for the presence of ova or parasites.

For burial, the bodies were usually flexed and placed in crude feather-down bags or under pieces of baskets. In or near the body were deposited various objects which were mute evidence of the meagerness of the food and clothes which these people possessed. They apparently cultivated corn, sunflowers, gourds, pumpkins, squash, pigweed, lambs-quarters, and beans, presumably for food, as many of these seeds were found in the caches. They had means of procuring fish, mammals and birds, as many bones of these animals were found in the caches and in the bluffs which these people inhabited. Thus, the data obtained from the caches indicate that these people lived on a mixed diet, if they ate what we assume they did. In the case of one of these people, we do not have to assume what was eaten during the last days of life. In an exceptionally dry shelter, where characteristic caches were found, there was a part of a dried body. The tissues of the lower part of the abdomen, pelvis, left leg to the middle third of the thigh, and the right leg and foot were dried and shrunken but well enough preserved so that the distal third of the large blood vessels of the abdomen, the sigmoid flexure of the colon, and the rectum could be definitely identified.

* Research Series No 411 Received for publication Jan 6, 1936

From the Division of Medicine, The Mayo Clinic, and the Department of Zoology, University of Arkansas

In the rectosigmoid or rectum were dried pellets of feces (figure 1), which were removed by means of long tissue forceps. The situation of this material obviates any question as to its true nature. The only questionable feature is whether this person might not have been buried more recently than has been assumed.

The present natives of this district do not bury their dead in these shelters. The American Indian in this part of the country did not utilize these shelters for any known purposes. There were no "top layer cultures" in any shelters of this immediate district. A fugitive from justice might be considered as a possibility. This possibility is ruled out because the remains from which the feces were obtained were those of an elderly woman.

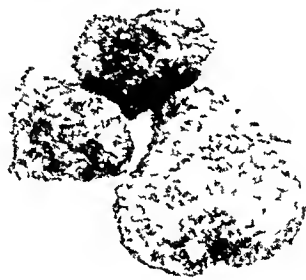


FIG. 1 Pellets of feces obtained from mummified body

The identification of the remnants of food particles in the feces was most interesting. This work was done at the Bureau of Biological Survey, United States Department of Agriculture, by Clarence Cottam and his staff, who are in charge of Food Habits and Wild Life Research. They were aided by various members of other divisions and bureaus. The report was as follows: "Our office has examined the material and we find that the principal food item consisted of the fruit of the sumac (*Rhus? Capallina*). The other common food item consisted of ground acorns (*Quercus*), apparently black oak (*Quercus velutina*). Incidentally this is a common species of oak occurring in Arkansas. In addition to these two items, there seems to be a little unidentifiable vegetable material, perhaps from some fruit substance. There was also a fair amount of charcoal which may have been eaten deliberately or mixed with the food. At any rate it was well mixed with the material submitted.

"Within the intestinal material were two small early stage coleopterous larvae of the family Nitidulidae. Dr. A. G. Boying of the Bureau of Entomology and Plant Quarantine believes that these probably belong to the genus *Stelodite*. Most species of this family of small beetles feed on the juices of fruits, fermenting sap, dried or stored fruits, and a few feed on flowers, fungi and carrion.

"The photograph (figure 2) accompanying your letter is stated by Dr. H. W. Ewing of the Bureau of Entomology and Plant Quarantine to represent some species of mite of the family Tyroglyphidae. Members of this family feed largely on stored food products and decaying materials.



FIG. 2. Photomicrograph of insect contained in the feces.

"In addition to these, a fragment of an ant (*Formicidae*) and a number of lice and mites have been transmitted to specialists for further study. I will communicate with you further as soon as we obtain more specific identification of the minute items held out.

"A fungus growth was found on some of the material which undoubtedly developed after the individual was buried. It seems entirely possible that the insect material may have been taken accidentally or incidentally with the food and probably as a result of not being unduly selective in the choice, nor insisting on a high degree of sanitation. It seems probable that this represents a winter food."

The report on the foregoing material was as follows "Coleopterous larva belonging either to the family Nitidulidae or one of the small families relating to the Nitidulidae, possibly the Monotomidae. Definite determination cannot be given from the two fragments. Det. A. G. Boving.

"A few specimens of a species of *Cheyletus*, a predacious mite that feeds largely on other mites.

"Fragments of a species of the family Tyroglyphidae. Det. H. E. Ewing."

We were very anxious to find intestinal ova or parasites, if any were present. Many searches of the material have been made by Dr. T. B. Magath, but all these failed to reveal ova or parasites. A pellet of the feces was cracked and cultures were made from the center, but neither spore-forming nor non-spore-forming microorganisms grew. Tests for bile were negative. Quantitative chemical analyses of the feces were done by Dr. Mildred Adams, the results of these analyses are shown in table 1.

CHEMICAL ANALYSES OF FECES OF AN OZARK BLUFF DWELLER AND FECES OF A NORMAL PERSON

	Normal Feces Percentage of Dried Weight	Feces of an Ozark Dweller Percentage of Dried Weight
Nitrogen	5.10	4.77
Calcium	3.10	4.37
Magnesium	0.67	0.50
Sodium	1.00	0.67
Potassium	2.00	3.92
Phosphorus	1.70	1.63

Several of the crude cradles obtained from these shelters during the excavations were smeared with material which probably was feces. In this material there was an occasional insect, but nothing which resembled food material, intestinal ova, or parasites.

We have objective data which indicate that these people ate the fruit of the sumac, and acorns. We have circumstantial evidence that they ate corn, pumpkins, squash, sunflowers, lambs-quarters and beans, and the flesh of mammals, fish and birds. One can imagine that the food supply of these people was uncertain. However, they stored many of the natural foods which were gathered from the forests, such as hickory nuts, chincapins and acorns, and then cultivated crops of corn, sunflowers and other seeds for winter consumption and spring planting. These crops must at times have been limited and uncertain. These people did not possess sufficient implements to carry on more than a limited amount of agriculture, nor did they possess sufficient weapons to obtain a very great amount of meat by hunting. Their hunting equipment consisted of spears, darts, crude axes, and, of course, sticks and stones. It is of sufficient importance here to mention the fact that almost invariably they split the bones of the animals utilized for meat, in order to obtain the marrow for food. This splitting of the bones was probably done on account of the scarcity of meat.

The teeth of both the children and the adults were generally very good (figure 3). There was no evidence of either congenital or acquired diseases.

At the present time, it is recognized that ossification occurs earlier among females than it does among males. In the newly born this difference of ossification may be one of days, while later in life the time at which fusion of the epiphysis occurs may differ by years in the two sexes. There is some evidence to suggest that ossification occurs earlier among children who are well cared for than it does among children who are neglected and underfed.

Many factors appear to influence ossification, which is the determining influence on normal shape and size of the adult bone. Some of these factors are fresh air, food, sunlight (or ultraviolet light) and exercise. Ossification is advanced in certain conditions, such as pubertas praecox, and



FIG 3 Teeth of an adult of this race

is retarded in disorders of certain endocrine glands, such as dysfunction of the thyroid gland or pituitary body.

It is evident that the bluff dwellers possessed all the necessary requisites for the production of normal skeletal systems. Food may have been abundant enough at times, but the supply was uncertain. The food supply of the growing children after the period of nursing undoubtedly was uncertain, and according to present standards, it was meager; however, normal skeletons did develop. The possible influences of dysfunction of the thyroid gland or pituitary body have been carefully considered. There were no examples of disturbances in growth and development which would suggest dysfunction of these glands.

The femurs and tibias of a child were put aside for study on account of their lightness of weight and increased transverse diameters at the distal ends. So light and fragile were these bones that great care had to be ex-

excised in handling them, and in spite of this care the lower end of the right femur was broken. Satisfactory roentgenograms were difficult to obtain on account of the thinness of these bones. At the distal ends of these femurs and at both ends of the tibias there were dense transverse lines in the roentgenograms, otherwise the roentgenologic appearance of these bones was normal. These lines serve to indicate periods of growth. In the absence of any more marked deformities than were present in the lower ends of



FIG 4 Maximal amount of anterior bowing of tibias of this race

these femurs or in their condyles, and because of the minimal degree of anterior bowing of the tibiae, a definite diagnosis could not be made. However, these bones were not normal, and without doubt this child had suffered a prolonged illness with secondary dietary deficiencies.

There were two adult tibiae which showed anterior bowing and which were suggestive of rickets (figure 4).

The infant and adult skeletal remains of this primitive race of Americans impressed one by the absence of good evidence of rickets, scurvy and endocrine diseases or evidence of secondary deficiency diseases, which are common among present races. This absence of evidence of deficiency diseases is still more striking when one considers the possible effects of uncertain food supplies during that all important period of growth and development from five to ten years of age. The conclusion to be drawn is that this race possessed indomitable qualities in their germ plasma for the development of normal skeletons under adverse conditions and that this race also possessed a remarkable flexibility of digestive apparatus, which permitted them to eat large quantities of inferior, and perhaps unclean food and to utilize from it the so-called essentials of a normal diet. In other words, perhaps what is ingested in the way of food is not so important as how it is utilized in the process of alimentation and absorption.

The absence of findings indicating the presence of deficiency diseases in the Ozark bluff dweller is in keeping with studies made on other primitive races.¹

SUMMARY

The undigested food residue contained in the feces of an Ozark bluff dweller consisted of the fruit of the sumac, acorns, and insects. Their remains indicate that they had existed on a mixed diet of vegetable materials, meat and fish. No good evidence of primary dietary or endocrine deficiency diseases was found. This race must have possessed an indomitable germ plasma to be able to produce and maintain normal skeletal parts without evidence of deficiency diseases under most adverse dietary and sanitary conditions.

BIBLIOGRAPHY

- 1 MOODIE, R. L. Roentgenologic studies of Egyptian and Peruvian mummies (Anthropology, memoirs). Field Museum of Natural History, Chicago. Vol. III, 1931, 66 pp.

CASE REPORTS

TERMINAL HEMORRHAGIC NEPHRITIS A CASE EXEMPLIFYING THE PROTEAN CHARACTER OF ITS SIGNS AND SYMPTOMS*

By IRVINE H PAGE, *New York, N Y*

CHRONIC hemorrhagic nephritis is a disease exhibiting signs and symptoms of protean character. So elusive are many of these that prognosis and effects of various treatments are often seriously misjudged. It is for this reason that the record of this patient, illustrating many of these pitfalls, is presented.

The Patient This patient, a 49 year old woman, complained of swelling of the ankles beginning three years ago. The past history was irrelevant. Edema of the ankles began insidiously and was not associated with an obvious infection. Arterial pressure was found to be 200/120 mm of Hg. Dr Francis O'Connor, of Kingston, New York, who kindly referred her to us, has written that she complained at that time of severe headaches, spots before the eyes, and scanty urine. Red cells, casts, and protein were found in the urine. She was able to continue her work, but nine months later she seemed to be entering the terminal stage of nephritis. The blood pressure was 220/130 mm, non-protein nitrogen 44 mg per cent, and creatinine 2.9 mg per cent. Two months later she was admitted to this hospital.

She was a small woman appearing chronically ill and markedly anemic. Except for a slight amount of perivascularitis near the discs, the fundi were normal. All teeth had been removed. The heart was not overactive, nor was it enlarged. A₂ was accentuated and there was a soft systolic murmur heard over the apex. Arterial blood pressure was 196/110 mm of Hg. Slight edema of the sacrum, ankles and legs (grade 2) was present.

The electrocardiogram showed the T-waves diphasic in Lead I, and negative in Leads II and III. R₂ was split and R₃ was both split and of low voltage. Atrio-ventricular conduction time was 0.22 second.

Renal efficiency, as measured by the urea clearance test of Moller, McIntosh and Van Slyke,¹ as recently described by Van Slyke, Page, Hiller, and Kirk,² was reduced to 13 per cent of normal. The maximum ability to concentrate glomerular filtrate as measured by the specific gravity of the urine was 1.009. Correction was made for the protein present in the urine, that is 0.003 subtracted from the total specific gravity for each 1 per cent of protein. The number of formed elements in the urine was estimated by the technic of Addis.³ On admission, 3,200,000 red blood cells were found in a 12-hour specimen of urine passed during the latter half of a 24 hour period, during which the patient received no fluids, 500,000 red blood cells are considered the upper limit of normal. Casts numbered 684,000, of which 80 per cent were granular and 20 per cent hyaline. Protein in the urine was estimated by the method of Shevky and Stafford.⁴ The excretion amounted to 6 grams in 24 hours. Hemoglobin as recorded in terms of volumes per cent of oxygen capacity was reduced to

* Received for publication October 2, 1935.

From the Hospital of the Rockefeller Institute for Medical Research, New York, N Y.

14.8, while 19.0 is the normal value for a woman of her age (see Peters and Van Slyke⁵). Gastric analysis showed free hydrochloric acid was not present even after histamine. Total acid was low, averaging only 7.0

Gastric Analysis	Volume cc	Free HCl	Total Acid
Fasting	12	0	5.8
20 minutes after alcohol	17	0	7.4
40 minutes after alcohol	18	0	9.6
20 minutes after histamine	13	0	9.3

THE COURSE

1 Edema, Plasma Proteins, Urinary Proteins and Diet A diet of 2200 calories containing 80 grams of protein and 1.0 gram of salt was prescribed. Usually about one-half of the protein consisted of casein. Although the total plasma proteins were reduced to the level at which edema may appear, the albumin fraction was above the edema level. Fifteen days after admission the edema almost disappeared without a significant rise in either total plasma proteins or plasma albumin. This result was probably due to withdrawal of salt from the diet. Protein in the diet was raised to 100 grams. Urinary excretion of protein varied from 5 to 7 grams in 24 hours. After approximately one month, the dietary protein was reduced to 20 grams making up the deficiency of calories with carbohydrate. After 45 days of this regime no significant change in plasma proteins occurred, but urinary excretion fell slightly to 3 to 4 grams in 24 hours. Again the protein in the diet was raised to 100 grams and maintained at this level for five months. A slight rise occurred in the total plasma proteins, but no significant change was observed in the albumin fraction. Urinary protein excretion rose 5 to 6 grams, but fell toward the end of the period to an average of 2 to 3 grams. The protein in the diet was again reduced, this time to 30 grams, and maintained at this level for 4½ months, but no significant reduction of plasma or urinary proteins occurred. Two months after this period had started the patient had a severe hemorrhage from the descending colon which caused temporary slight depression of plasma protein. The following 11 months no restriction was put on her diet except that it contained the usual amounts of meat, and free salt was avoided.

This patient illustrates the fact that in patients who are well nourished and not losing large amounts of protein in the urine, protein in the diet may be varied within wide ranges without significantly affecting the plasma protein level or its excretion in the urine. But she remained free of edema only so long as salt was allowed in small amounts. It is of interest that although for 13 months the patient received not more than 1.5 gram of salt in her diet and excreted little more than a gram in 24 hours in the urine, she showed no signs of chloride deprivation. Examination of the serum after nine months on this low chloride intake showed that the chlorides were not significantly reduced, that is, 99.7 milli-equivalents per liter at pH 7.31.

2 Renal Efficiency The urea clearance remained well below the level of 20 per cent of normal, which is the level set by Van Slyke and his associates⁶ as that below which uremia may be expected to supervene. Except for insignificant variations, an average level of 10 per cent of normal was maintained for at least 19 months. Ability to concentrate urine was also reduced to a minimum.

3 Hemoglobin and Hematuria Throughout the course in the hospital the hemoglobin fell slowly from 14.5 volumes per cent O₂ capacity to 11.2 shortly before death. A hemorrhage from the lower colon caused considerable loss at one time, but within two months it had regenerated to its original level. Reduced iron (3 grams a day) was fed during this period and may have aided in regeneration. Iron fed over a two-month period prior to this (the seventh and eighth months in the chart) had no significant influence on the level of hemoglobin. Hematuria was not pronounced until two months prior to death. Usually, however, the number of red cells excreted was

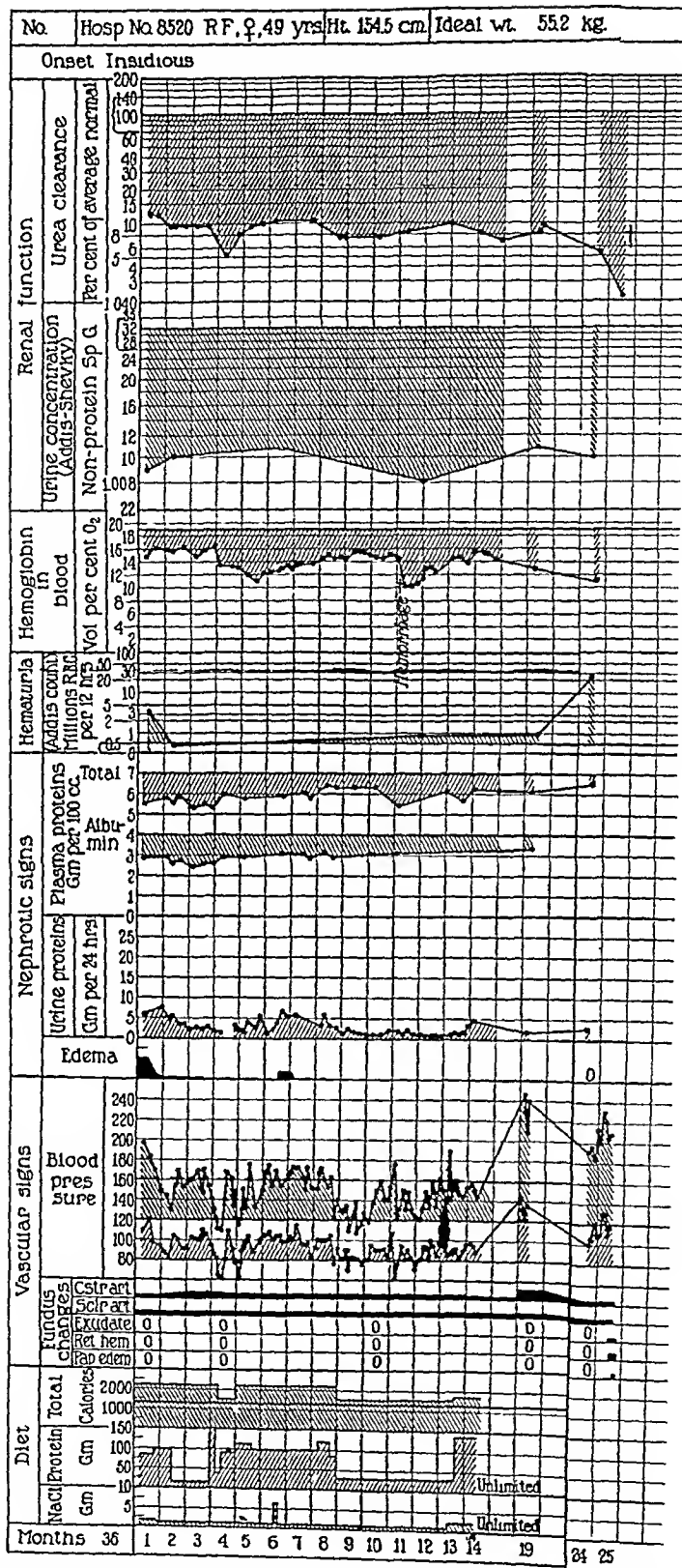


FIG 1 Course of the patient as observed in the hospital. Blood pressure measurements were taken daily with patient in bed. They were averaged for convenience in charting. Fundus changes are represented as (a) arteriolar constriction, (b) sclerosis, (c) exudate, (d) hemorrhage, (e) papilledema. The first figure following the word "months" on the bottom line of the chart represents the probable date of onset.

slightly above normal. The loss of hemoglobin in the urine, at least as measured by the number of red blood cells, could not have contributed materially to the anemia.

4 Blood Pressure, Eyeground and Electrocardiographic Changes Fluctuations in arterial blood pressure were great. For periods of weeks it was normal, only to rise again to an abnormal height. During the terminal six months it rose markedly and maintained the high level until just before death. Slight constriction of the retinal arterioles was usually observed. Sclerotic changes in them were also present, but of very moderate degree. It is of especial interest that not until a few days before death were hemorrhage, exudate, and papilledema noted.

The electrocardiograph changes were as follows:

On admission, T_1 diphasic, T_2 negative, T_3 negative, R_2 split, R_3 split and low voltage, conduction time 0.22 second.

Eighteen months later, T_1 negative, T_2 positive, T_3 positive, R_3 split and low voltage, conduction time 0.16 second.

Twenty-four months later, T_1 positive, I_2 diphasic, I_3 negative, R and S_1 low voltage, conduction time 0.18 second.

Although it was suggested on the basis of the prolonged conduction time that bundle branch block might develop, this did not occur. The size of the heart increased but moderately. Twenty days before death the measurements from a roentgen-ray plate were, maximum left 97 cm, maximum right 65 cm, and internal chest diameter 26.0 cm.

Terminal Stage The terminal stage was of more than usual interest because of the long period of almost complete anuria during which she had but few symptoms. Four months prior to death she withstood an attack of bronchopneumonia in the North Country Community Hospital. Two months later vomiting began. It varied in intensity, but in general became progressively worse. Eighteen days before death the output of urine began to diminish and three days later had fallen to a low level (figure 2). As fluid intake was not reduced, her weight increased only to fall sharply five days before death.

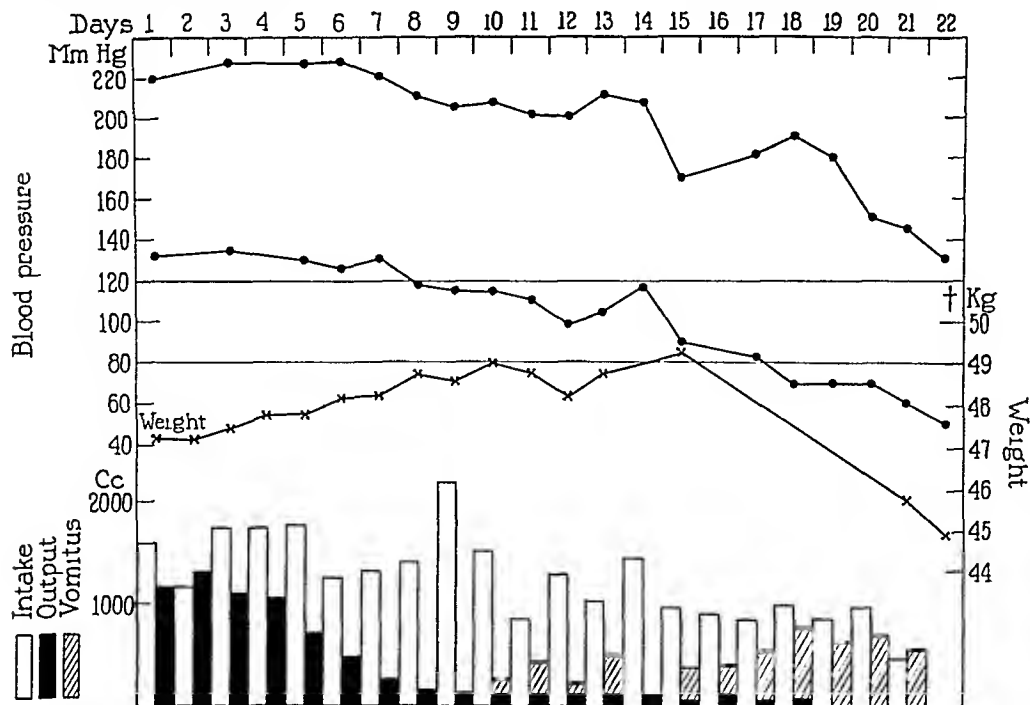


FIG 2 Blood pressure, weight and fluid intake and output during terminal period in which almost complete anuria occurred.

Ten days before death urea clearance was 12 per cent of normal, and blood urea nitrogen 155.6 mg per cent. Little change was noted in ability to concentrate urine, but marked hematuria had appeared. Hemoglobin was somewhat more reduced and plasma proteins a little increased. Blood pressure had risen from an average level of 156/98 to 242/140 mm of Hg. Constriction of the arterioles of the fundi was more marked. About one month before death the eyegrounds were normal except



FIG 3 Section of kidney showing marked thickening of the blood vessels, atrophied and dilated tubules, loss of glomeruli, hyaline scars, and interstitial sclerosis

for slight arteriolar sclerosis and faint hyperemia of the nerve heads. Examination made the day before death showed that a few small fresh hemorrhages and early patches of exudate were present. There was no papilledema. Constriction of the arterioles was less marked than that observed in the previous examination.

She complained from time to time of pain in the stomach and moderate rectal bleeding. She was moderately clear mentally up to death. A few days before it she exhibited periods of Cheyne-Stokes respiration and a little dyspnea. An attempt was made to promote urine excretion by means of glucose given intravenously (500 cc) with 10 per cent of 95 per cent alcohol added. No diuresis resulted, but the patient had a long restful sleep. One day before death the content of CO₂ in the serum was 13.47 millimols per liter at pH 7.13. The serum chloride was 90.5 milli-equivalents.

During the morning of the day of her death slight fibrillary twitching was observed, but except for nausea she had no complaints.

Autopsy (Dr. C. P. Rhoads), 4-1/2 Hours Postmortem. The findings of especial interest during the gross examination of the body were, absence of pericardial effusion, marked left ventricular hypertrophy (weight 480 grams) and diffuse atherosclerosis of the coronary vessels. In many places the intima of these vessels had become thin and brittle. Throughout the aorta, confluent atherosclerotic patches were present. There was marked emphysema of the lungs. The vessels of the spleen were markedly thickened. The mucous membrane of the stomach and intestine was edematous and deeply injected. Extending from the duodenum to the end of the large intestine there were many areas which were deeply injected, in the center of which were shallow ulcerations (10 to 30 cm. in diameter) extending through the mucosa and covered with yellow exudate. The sternal bone marrow was pale brick red in color and fairly cellular. No gross abnormality was observed in the brain or pituitary gland.

The left kidney weighed 32 grams and the right 38 grams. Both were markedly reduced in size. The capsules stripped with difficulty leaving an irregular contracted surface. The cortex was 10 to 30 mm. in width. Branches of the renal artery showed markedly thickened walls.

Microscopic examination showed that marked intimal sclerosis with necrosis and formation of cellular, sclerotic scars was present in the coronary vessels. Most of the vessels in the spleen and liver showed sclerosis. Very striking increase in the number of basophilic cells in the anterior lobe of the pituitary gland was present. Chromophobe cells were few in number, while acidophile cells were numerous.

Sections of the kidney (figure 3) showed extremely advanced sclerosis and infiltration of interstitial tissue with lymphocytes. Many glomeruli had disappeared and others were converted into hyaline scar tissue. Others exhibited hyaline thickening of the capillary wall with proliferation of epithelial and endothelial cells, and decrease of intravascular red blood cells. The tubules were atrophied and dilated, many containing a basophilic exudate. The arteries and arterioles presented most marked morbid change. Very marked fibrous intimal thickening was present along with hyaline change of the nuclei, with almost complete occlusion in many instances.

DISCUSSION

Onset of the disease was insidious in character. Gross hematuria, headache, fever and evidence of infection—so characteristic of the acute onset—were lacking. She was not aware that she was ill until swelling of the ankles occurred. By that time the blood pressure was elevated to 200/120 mm. of Hg, indicating, probably, that the morbid process was already of months' or years' standing. It has been the experience in this clinic that those patients in whom the onset is insidious are likely to die usually within a few years, contrasting with those in whom the onset is stormy, many of whom recover completely.

When she was first seen in this clinic she had entered the terminal stage Van Slyke and his associates⁶ define this as the stage during which urea clearance is below 20 per cent of normal and uremia may supervene at any time. Usually it lasts less than a year, but, as this patient illustrates, may continue for 20 months or more.

Physical examination showed that she was in a poor state of nutrition. A diet, liberal both as to calories and protein content, rapidly brought improvement. She was able to maintain good nutrition until within a few weeks of death. Coincident with improvement of nutrition was a feeling of well being. It is our belief that if patients with nephritis are properly nourished they may enjoy life to within weeks or months of death.

Since edema was almost the only symptom of which she complained, it was desirable to rid her of it. Excretion of protein in the urine was not great, but nevertheless she was unable to keep the plasma protein at a normal level, probably due to inability to synthesize them. Edema in this case appeared to be largely due to salt, for if it were withdrawn the edema disappeared and reappeared on resuming it. A diet containing 100 grams of protein for one month did not cause the plasma proteins to rise, nor did an isocaloric one containing 20 grams fed for 45 days cause them to fall. Again the high protein diet was resumed, this time for five months, without significantly affecting them. Reduction of protein to 30 grams for a period of 4½ months followed, again without effect. Nor was any close relationship found between the level of protein in the diet and excretion of protein in the urine. It appears that in this patient, who was well nourished, protein intake of from 20 to 30 grams covered the amount lost in the urine and the requirements of the tissues, but that even 80 to 100 grams were unable to raise the level of the plasma proteins. It is for this reason that it was our belief that ability to synthesize them was impaired.

Since it was necessary to interdict salt in the diet, an excellent opportunity was afforded to observe the effects of its deprivation. For 19 months she received little more than a gram of it a day. This was controlled by estimation of the salt content of the urine two days of each week. At no time were symptoms referable to its withdrawal evident, nor did the chloride in the serum fall below the lower limits of normal. Since polyuria was not present it appears that she did not wash out sufficient tissue chlorides to cause symptoms of hypochloremia.

Anemia was not marked until shortly before death. It appears to be of significance that the hemoglobin fell slowly. It is often observed that rapid diminution of hemoglobin may be associated with early termination of the patient's life. Large doses of reduced iron did not increase hemoglobin, but following a hemorrhage it appeared to aid in its recovery to the level maintained before the hemorrhage. Hematuria was never sufficient to contribute to the anemia.

The periods of marked hypertension alternating with those during which arterial pressure was nearly normal are of interest. One might well have been deluded into thinking that therapeutic success had been achieved were treatment to have been instituted at a time coincidental with the naturally occurring pressure reduction. Such more or less rhythmic changes recurring within a cycle of weeks or months are not rarely observed in this clinic. Changes in arterial pressure were unaccompanied by changes in renal efficiency as measured by urea clearance.

Morbid changes in the eyegrounds were limited to arteriolar constriction until weeks or days before death, when both exudate and hemorrhages appeared. We believe this to be an especially good prognostic sign. Lack of fundus changes often aids in differentiating the terminal stage of malignant hypertension from that of hemorrhagic nephritis. In the former profound changes may be the presenting symptom from onset of the disease, and always are observed in the terminal stage. Exudation, destruction of vessels, old and new hemorrhages and papilledema characterize these changes. Although similar changes may be observed in the fundi of a nephritic patient, they often follow the course illustrated by this patient. It is then that fundus examination is of differential diagnostic value.

The vascular system of this patient, including the heart, withstood the hypertension well. Although the arterial pressure was often higher than may be observed in cases of malignant hypertension, the heart enlarged slowly and caused but a minimal number of symptoms. The electrocardiograph showed, however, that damage was occurring. Autopsy confirmed the belief that the morbid changes in the blood vessels were extensive. They consisted of sclerosis and deposition of lipids without the hemorrhages into the vessel wall which are so often observed in malignant hypertension.

She suffered from oliguria approaching anuria for 18 days before death. In spite of this and a marked rise in retention products in the blood, there were few classical symptoms of uremia except vomiting. Only on the last few days were occasional fibrillary twitching of the muscles and a little drowsiness observed. It is a matter of surprise that a patient who for 19 months or more had suffered from severely restricted renal efficiency was able to withstand 15 days of almost complete anuria without exhibiting many symptoms or signs. Anuria resulting from a surgical procedure or that occurring during the acute stage of nephritis may end fatally in shorter periods.

Autopsy revealed two facts of interest which are not usual in such cases, and for which we have no explanation. The first was the presence in the anterior lobe of the pituitary gland of an increased number of basophile cells. The second was the absence of pericarditis, either old or fresh.

SUMMARY

A case of terminal hemorrhagic nephritis has been presented to illustrate the elusive nature of the signs and symptoms and their relationship to diagnosis and prognosis. The following points were especially well exemplified.

1. An insidious onset usually means a fatal termination of the disease.
2. The terminal stage (urea clearance less than 20 per cent of normal) may last for many months and at times more than a year.
3. Poor nutrition contributes to the discomfort and ill health of the patient. Good nutrition may spell the difference between well being and invalidism. Protein should be sufficient to cover the needs of the tissues and to replace that lost in the urine. High protein feedings need not restore the plasma protein level to normal, nor low protein diets reduce it. It is assumed that the ability of some patients to synthesize plasma proteins is impaired.
4. Interdiction of salt may abolish edema even though plasma proteins do not rise above the level at which edema may occur. If polyuria does not occur with

washing out of large quantities of tissue chlorides, chloride restriction may be as extreme as little over one gram without producing symptoms of hypochloremia or significantly reducing the chloride in serum

5 Even when hemoglobin is not markedly reduced and further reduction is slow, death may occur in uremia. Administration of iron will not affect its level except under certain special circumstances such as hemorrhage when it appears to aid in regeneration of the lost hemoglobin

6 Arterial blood pressure may alternate between being markedly elevated for periods of weeks or months and being almost normal. This is peculiarly deceptive when treatment designed to lower blood pressure is being investigated. Associated changes in renal efficiency as measured by urea clearance do not occur

7 Morbid changes in the eyegrounds other than arteriolar constriction may not be present until weeks or days before death, aiding thus in the differential diagnosis from malignant hypertension in which fundus changes are always advanced in the terminal stage and usually during its onset

8 Oliguria approaching anuria may last for relatively long periods (18 days) in spite of a preliminary period of severe renal inefficiency without producing marked signs or symptoms

9 An increased number of basophile cells may be found in the pituitary gland

BIBLIOGRAPHY

- 1 MOLLER, E, McINTOSH, J F, and VAN SLYKE, D D. Studies of urea excretion. IV. Relationship between urine volume and rate of urea excretion by patients with Bright's disease, Jr Clin Invest, 1928, vi, 485
- 2 VAN SLYKE, D D, PAGE, I H, HILLER, A, and KIRK, E. Studies of urea excretion. IX. Comparison of urea clearances calculated from the excretion of urea, of urea plus ammonia, and of nitrogen determinable by hypobromide, Jr Clin Invest, 1935, xiv, 901-910
- 3 ADDIS, T. The number of formed elements in the urinary sediment of normal individuals, Jr Clin Invest, 1926, ii, 409
- 4 SHEVSKY, M C, and STAFFORD, D D. A clinical method for the estimation of protein in urine and other body fluids, Arch Int Med, 1923, xxvii, 222
- 5 PETERS, J P and VAN SLYKE, D D. Quantitative clinical chemistry, Vol I. Interpretations, 1931, Williams and Wilkins, Baltimore
- 6 VAN SLYKE, D D, STILLMAN, E, MOLLER, E, EHRLICH, E, McINTOSH, J F, MACKAY, E M, HANNON, R R, MOORE, N S, and JOHNSTON, C. Observations on the courses of different types of Bright's disease, and on the resultant changes in renal anatomy, Medicine, 1930, ix, 257
- 7 PAGE, I H. The effect on renal efficiency of lowering arterial blood pressure in cases of essential hypertension and nephritis, Jr Clin Invest, 1934, xiii, 909

TONSILLITIS ASSOCIATED WITH ACUTE ASEPTIC MENINGITIS *

By DAVID RIESMAN, M D, Sc D, F A C P, *Philadelphia, Pennsylvania*

CASE REPORTS

Case 1 Mr I B, a married man of 45 years, a native of New York City, had always enjoyed good health. On Tuesday, April 4, 1933, he awoke with a severe headache and a sore throat. The headache was obstinate, not yielding to codeine.

* Read before the Section on Medicine of the College of Physicians of Philadelphia, February 25 1935 with additions

or other anodynes Sinus roentgen-ray and blood Wassermann test were negative The blood count was entirely normal, the fasting sugar 120 mg per 100 c c of blood The tendon reflexes were exaggerated on the right side and the Babinski reflex was present on that side Eye ground examination showed dilated vessels but no papilledema Lumbar puncture revealed the following Pressure 22 mm of mercury, globulin increased, sugar 554 mg, Wassermann and colloidal gold tests negative The cell count was surprising—there were 1125 cells to the cubic mm The fluid was sterile on culture

I had the opportunity of seeing Mr B with his physicians Drs Goodheart and Ginsburg, on April 9 The notes of the result of my examination are as follows

The patient looks ill and is exceedingly apprehensive, perhaps because of the persistent headache, perhaps because of the many examinations and tests which the obscurity of his illness has rendered necessary The headache is apparently very severe and he is inclined to dig his head into the pillow The pupils are slightly unequal, markedly contracted but react to light, all ocular movements are normal The tongue is covered with a thick white coating Over the right tonsil a whitish exudate is visible like that of follicular tonsillitis, the left tonsil cannot be seen satisfactorily The heart and lungs are normal The liver is a little enlarged, the abdomen slightly distended, the suprapubic region dull on percussion, the spleen is not palpable The knee jerk is normal, the Babinski reflex is absent, but there is a suggestion of an ankle clonus on both sides While there is no real ataxia of the arms, the tips of the fingers are not easily brought together The knee-heel test is normal There is no rigidity of the neck, no Kernig sign The eye grounds are normal The temperature is 102 to 104°, blood pressure 122 systolic 70 diastolic, the pulse ranges from 70 to 90, respiration 20 The leukocytes in the blood are 16000 per cubic mm

On questioning the patient I obtained information about an incident that may have had considerable bearing upon his case On April 1, three days before the onset of the illness, he had been unexpectedly called to the home of an aged uncle When he arrived he found his relative lying dead on the floor It was the first death he had ever seen and the shock was, as he expressed it, terrible It would not seem to be an unwarranted assumption that this psychic trauma had something to do with the localization of the poison in the cerebral meninges

I was of the opinion that the tonsillitis was the primary element in Mr B's case and that with its subsidence the meningitic symptoms would also disappear As a therapeutic measure I advised the application of leeches to the mastoid processes Recovery was rapid, the patient leaving the hospital on April 14 On April 27 he came to see me in my office in Philadelphia He felt fairly well but still had some ringing in the ears, a feeling of a "kink" in the back of the neck and occasionally weak spells, relieved by lying down He was nervous, irritable and easily upset Physical examination revealed nothing of significance except a momentary ankle clonus on both sides but no Babinski reflex I have heard of the patient since then He is entirely well

Case 2 The second case occurred at the Children's Hospital in the service of Dr Joseph Stokes, through whose courtesy I am privileged to include it in this report The patient was a boy of four years, of Italian parentage, who apparently as the result of some birth injury had had convulsions up to the age of three years They then ceased and the child was subjectively normal until one day in May 1933, when he suddenly became feverish and had a convulsion His breathing was of the Biot type, temperature 102 The limbs were alternately rigid and relaxed, the Babinski reflex was present on both sides, no Kernig sign, some rigidity of the neck Examination of the throat showed a slight degree of tonsillitis Spinal puncture yielded a somewhat opalescent fluid, pressure 18 mm of mercury, globulin increased, sugar present, 500 cells to the cubic mm, nearly all were lymphocytes After the spinal puncture the child had no further convulsions A second puncture showed 1000 cells,

chiefly lymphocytes. There was no pellicle, and no organisms were found. Blood culture showed *Streptococcus viridans*, the Wassermann test was negative. The child's temperature became normal and the cell count in the spinal fluid was reduced to 10. A second blood culture again showed a profuse growth of *Streptococcus viridans*, but a third taken five days later was negative.

The diagnosis in this little boy was obscure but Dr. Stokes and his colleagues concluded that he had had a sterile meningitis, streptococcus tonsillitis and *Streptococcus viridans* septicemia without endocarditis. The child made a satisfactory recovery.

I am prompted to report these two cases because they illustrate certain unusual complications of acute tonsillitis. Although I did not see the first patient in the beginning nor the second one at any time, I believe the conclusion is justified that the tonsillitis was the primary disease.

The promptness of the recovery of both patients is unusual and puts this type of meningitis in a class by itself.

The literature is very meager on the subject of tonsillitis and meningitis. Krioll¹ is the only author among the many I have consulted who speaks of tonsillitis (angina) as a possible cause of acute serous meningitis. Cases of septic meningitis following tonsillitis, usually of the quinsy type are recorded. There are also references in the literature to encephalitis complicating tonsillitis. Fanny Halpern reported six cases, all in the female sex, of pontine-cerebellar encephalitis in persons ranging from 11 to 60 years. Halpern was unable to determine whether the inflammation of the brain was due to organisms or toxins of the tonsillitis or to a lessening of resistance to the encephalitis virus produced by the tonsillar infection. It must be remembered that the differential diagnosis of meningitis and encephalitis is sometimes difficult.

That there was a definite meningeal involvement in both the cases here reported cannot be doubted in view of a spinal fluid cell count of 1000 in one and 1100 in the other. As the fluid was sterile, I was inclined to the opinion that a virus might have been responsible, although the action of a bacterial toxin could not be ruled out. The fact that the cases were "aseptic" brings them in line with a number of similar ones recorded within the last few years—those of Wallgren,² under the title of "Meningitis 'Aseptica' Acuta," of Viets and Watts,³ as "Aseptic (Lymphocytic) Meningitis" and of Dickens,⁴ under the same title. Dickens in his article asks the question whether he was dealing with "a new disease entity due to a filterable or nonfilterable virus." In 1934 Armstrong and Lilie⁵ called attention to a virus they had encountered in monkeys which had shown definite signs and symptoms of meningitis, mice and guinea-pigs proved also to be susceptible to the virus. In May of this year Rivers and Scott⁶ reported the isolation of a virus from two human cases of meningitis, and stated that the serum from these cases protected animals from the virus. Crossed serological tests indicate the identity of the two viruses, that of Armstrong and that of Rivers and Scott.*

Armstrong and Dickens† in four human cases of "aseptic" meningitis found that the blood serum obtained in one case three years and eleven months,

* The Armstrong-Rivers and Scott virus appears by serologic tests to be identical with a third virus, that of Traub, found in white mice.

† I want to express my thanks to Lieutenant Commander Dickens and to Dr. Charles Armstrong of the Public Health Service for letting me have a manuscript copy of their forthcoming article.

in one a year, in one three and a half years after the attack protected mice against the Armstrong virus. In the fourth case protective bodies were absent at the beginning of the illness, but appeared two months after the onset of the meningitis.

The clinical picture in these cases was similar to that of I B except that in the cases recorded by Dickens and Armstrong infections of the upper respiratory tract and not a well-defined tonsillitis preceded the onset of meningeal symptoms. The disease lasted from ten days to two weeks and left no residual features of any kind. In all these cases the cellular response of the spinal fluid was almost entirely lymphocytic. It is easy to see how such a cytologic finding might suggest the diagnosis of tuberculous meningitis. There is however, no pellicle and animal inoculation is negative. The sugar, chloride and urea content of the fluid is within normal range.

As far as our present knowledge goes the disease is self-limited and requires little treatment except lumbar puncture which is the best means of controlling the most distressing symptom the headache. As an adjunct to or substitute for lumbar puncture, leeching from the mastoid process may be tried.

It is desirable that those who hereafter see cases of aseptic meningitis* have laboratory tests made with the spinal fluid for the discovery of a possible virus and with the blood serum which in the virus cases ought to protect mice against the virus.

Meningeal symptoms are not rare in the acute infections of childhood and also in pneumonia. These symptoms are often attributed to meningism, whatever that may mean. If lumbar puncture is done in such cases, it may reveal a pleocytosis suggestive of acute lymphocytic meningitis†.

In conclusion I should like to say that as far as tonsillitis is concerned experience has long ago convinced me that it is a potentially serious disease and should be treated with more respect than is customary.

BIBLIOGRAPHY

- 1 KROLL, M. Die neuropathologischen Syndrome (zugleich Differentialdiagnostik der Nervenkrankheiten), 1929, J. Springer, Berlin, 456.
- 2 WALLGREN, A. Meningitis "aseptica" acuta, *Wien Arch f inn Med*, 1926, **xii**, 297-312.
- 3 VIETS, H. R., and WATTS, J. W. Aseptic (lymphocytic) meningitis, *Jr Am Med Assoc*, 1929, **xiii**, 1553-1555, Acute aseptic meningitis, *Jr Nerv and Ment Dis*, 1934, **lxv**, 253-273.
- 4 DICKENS, P. F. Aseptic (lymphocytic) meningitis, *U S Nav Med Bull*, 1932, **xxx**, 362-366.
- 5 ARMSTRONG, C., and LILLIE, R. D. Experimental lymphocytic choriomeningitis of monkeys and mice, *Pub Health Rep*, 1934, **xix**, 1019-1027.
- 6 RIVERS, T. M., and SCOTT, T. F. M. Meningitis in man caused by a filterable virus, *Science*, 1934, **lxvi**, 439-440.
- 7 ARMSTRONG, C., and DICKENS, P. F. Benign lymphocytic choriomeningitis, *Pub Health Rep*, 1935, **i**, 831-842.

* Armstrong and Dickens state that since in their opinion the affection is caused by a virus, "aseptic" is a misnomer and propose the term "acute lymphocytic choriomeningitis."

† Pleocytosis has been found in typhoid fever (Dr James P. Leake—personal communication).

INTERMITTENT HYDRARTHROSIS ASSOCIATED WITH UNDULANT FEVER

By JOHN C SHARPE, M D , *Omaha, Nebraska*

ARTHRALGIA has long been recognized as part of the symptom-complex of undulant fever. However, true arthritic changes associated with the disease have not been emphasized as a predominant feature. We have had the opportunity in the past few years to see several such cases, which form the basis of another paper¹ dealing with these rheumatic manifestations.

The following case is of sufficient rarity and interest to warrant its individual consideration.

CASE REPORT

History J F 25, white, male, grocery clerk, entered the University Hospital on December 12, 1934, complaining chiefly of pain and swelling of the knees. The family and past history were non-contributory. He had always enjoyed excellent health until the onset of the present illness five years before admission. At that time he had first noted pain and swelling of both knees, the right ankle and the right wrist joint which persisted for six weeks. During the following year, the pain and swelling of the knees came and went at irregular intervals. On two occasions aspiration of fluid from these joints was required for the relief of pain. He was not aware of any associated fever at that time. One year before entrance to the hospital, the pain and swelling of the knees returned and again required several aspirations of the joints for the relief of pain. From that time to the present, he had noted a definite intermittent character of the swelling. He had been aware of an evening rise of temperature, at times reaching 102°. He had had little or no appetite and had lost 20 pounds in weight. As the result of his difficulty in walking, he had been unable to work. Additional history revealed the facts that at the time of the onset of the first arthritic symptoms, he had lived on a farm in Nebraska where he had drunk raw cow's milk, and that there had been several instances of abortion in cattle on nearby farms.

Physical Examination Examination revealed a well developed but poorly nourished young man with a moderate pallor of the face and mucous membranes. The temperature was 100.4°, the pulse 90, the respirations 20, and the weight 117 pounds. The blood pressure was 120 systolic, and 70 diastolic. There was a suggestive bilateral exophthalmos. The tonsils were small and adherent. There was a moderate generalized lymphadenopathy present, especially of the axillary nodes. The thyroid was not enlarged. The lungs were clear to percussion and auscultation. The heart was not enlarged. The first sound at the apex was accentuated, followed by a short systolic murmur. The splenic tip was palpable 2 cm below the left costal margin. The liver was not enlarged. Examination of the joints showed some stiffness of the left elbow and some swelling of the right ankle. There was bilateral swelling of the knees (figure 1), the right measuring 37.5 cm, the left 35.5 cm in circumference. There was a definite patellar ballottement, a moderate limitation of motion and no local hyperemia of the overlying skin. The patient complained of pain in the knees only at the time the swelling reached its highest level. The remarkable feature of the case was the periodicity of the swelling which occurred at the same time in both knees, in seven to ten day cycles. The measurements of their circumferences varied from 0.5 cm to 6.0 cm. During the period of recession, the swelling never entirely

* Received for publication July 19, 1935.

From the Department of Medicine, University of Nebraska, College of Medicine, Omaha, Nebr.



FIG 1

disappeared from the right knee but occasionally did so on the left side. During the diagnostic study and progress of the case, daily noon-day measurements were recorded (figure 2).

Laboratory Examinations The blood showed a hemoglobin of 52 per cent, erythrocytes 3,440,000, leukocytes 5,000. The differential cell count was normal. The smear showed moderate anisocytosis and poikilocytosis. The bleeding and coagulation time were normal. The urine was normal, Wassermann reaction negative. The blood chemistry was normal. The basal metabolic rate was ± 18 . Roentgenograms of the knees (figure 3) were interpreted as showing rheumatoid arthritis of moderate degree. Agglutination with the Brucella group, by the Huddleston technic, was found to be positive in a dilution of 1-400. Repeated cultures of the blood, urine and synovial fluid for *Brucella abortus* and *melitensis* were negative after three weeks. The cultures were made on blood plates, brain broth, liver infusion. Duplicate cultures on the latter medium were incubated in an atmosphere containing CO_2 . A direct smear of the synovial fluid sediment showed many segmented neutrophils, but no bacteria could be observed.

Course The temperature was usually normal in the morning but would rise as high as 101° to 103° during the evening, usually accompanied by profuse sweating, occasionally chills. The increasing doses of undulant fever vaccine (Lederle), administered subcutaneously, caused little or no appreciable effect on either the dramatic intermittent swelling of the knees or the nocturnal rise of temperature. He was discharged from the hospital January 28, 1935, and then followed in the out-patient department where vaccine therapy was continued at bi-weekly intervals until a total

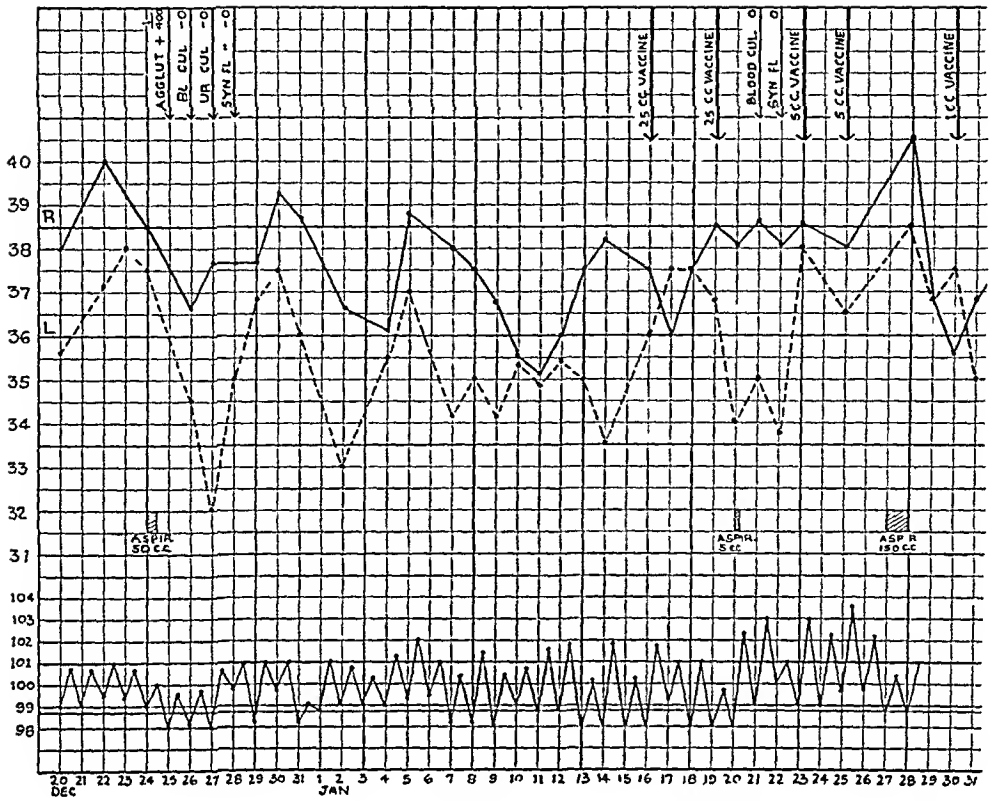


FIG 2 Intermittent Hydrarthrosis

(Continued on next page)

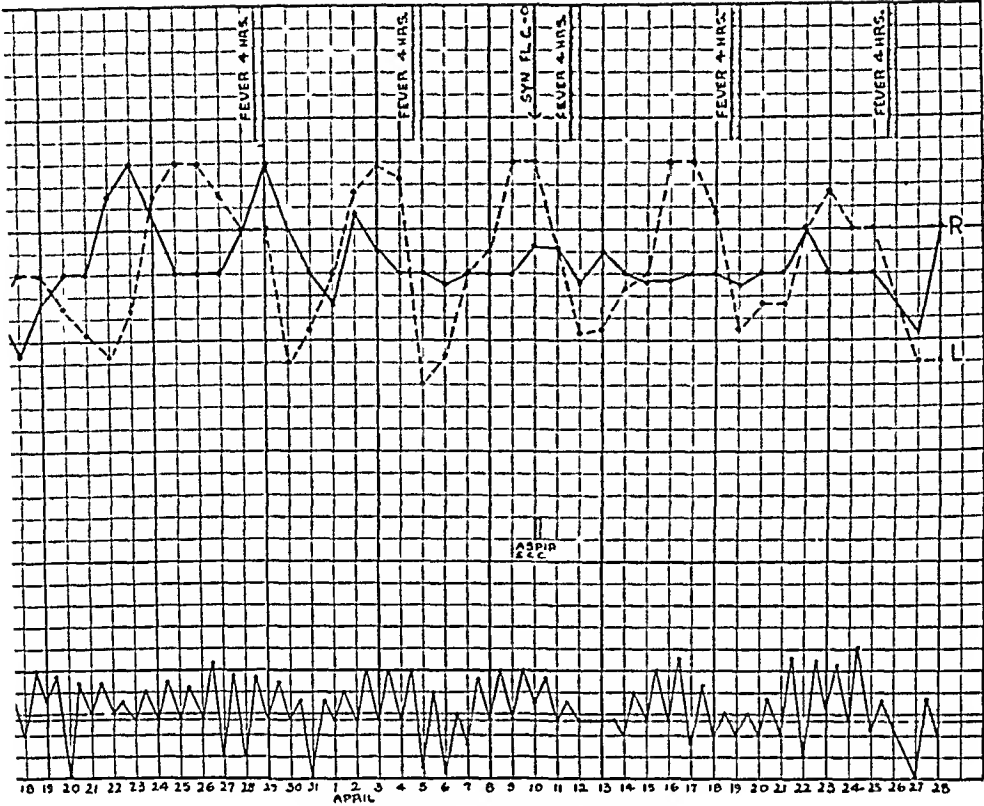


FIG 2 Intermittent Hydrarthrosis

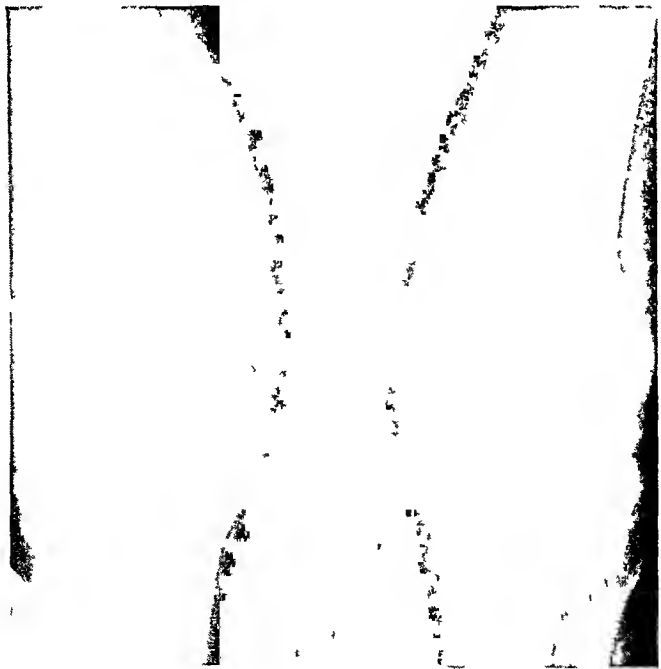


FIG 3

of 10 c.c. had been given. At the end of this time, there appeared to be slight but definite decrease in the fluctuations of the swelling of the knees, a moderate decrease in the evening temperature and an improvement in his general strength.

Further Course At the suggestion and under the direction of Dr. A. E. Bennett, Lutheran Hospital, Omaha, the patient was given a course of fever therapy by means of a Kettering hot air cabinet. Each weekly treatment consisted of raising the patient's temperature to 105° to 106° and maintaining it for four hours. During the first four weeks, the size of the knees varied widely, but after the fourth treatment the right knee remained approximately uniform in size, moderately swollen. The left knee continued the periodic swelling every six to eight days. The patient ceased to complain of pain in the knees, and there was less limitation of motion. There had also been a gain of eight pounds in weight. However, the evening rise of temperature continued, there was no improvement in the anemia, and the enlargement of the lymph nodes persisted as well as the splenomegaly. The agglutination reaction remained positive in dilutions of 1-500. Continued attempts to cultivate organisms from the synovial fluid were unsuccessful.

COMMENT

Because of our patient's loss of weight, the perspiration, the tachycardia, the moderate bilateral exophthalmos and the moderately increased basal metabolic rate, an associated hyperthyroidism was at first considered. Curtis² reports a patient with undulant fever complicating toxic goiter who improved greatly following operation. He emphasized the similarity of the symptoms of the two diseases. We have also seen such a case that improved following operation.

Up to the present time, there has been only one previous report of intermittent hydrarthrosis of the knees definitely proved to be due to *Brucella*. This case was reported by Baker³ in 1929 at the Johns Hopkins Hospital. His patient was a 47 year old Virginia man who, while slaughtering hogs, after an exposure to cold developed periodic swellings of both knees that continued for several months. The swellings were found to alternate precisely in seven day cycles. Although the agglutination reaction of the blood was at first negative, *Brucella abortus* was cultivated from the synovial fluid of both knees, the blood and the urine. Vaccine therapy was effective in reducing both the nocturnal temperature and the swelling of the knees, but only while the patient remained in the hospital. The hydrarthrosis reappeared when he returned to work which necessitated standing. Our case showed only moderate improvement following vaccine therapy and further slight improvement after seven fever treatments.

Baker suggested that infection by a member of the *Brucella* group of organisms might prove to be the cause of the interesting and rare clinical syndrome, intermittent hydrarthrosis. With this in mind we studied our patient, and while we were not able to prove definitely that the hydrarthrosis was due to *Brucella abortus* or *melitensis*, there was little doubt that our patient presented an active and persistent case of undulant fever. We are in accord with Baker in stating that because of the lack of uniformity of opinion regarding the etiology of intermittent hydrarthrosis and since many of the recorded cases give a history of "fever" simulating malaria and finally because two cases of undulant fever have now been reported associated with intermittent hydrarthrosis, further attempts to determine the relationship of the two conditions should be made.

SUMMARY

1 A second case of undulant fever associated with intermittent hydrarthrosis of the knees is reported. The history is of several years' duration.

2 Repeated attempts to cultivate *Brucella abortus* or *melitensis* from the synovial fluid, the blood and the urine were unsuccessful.

3 Only slight improvement followed courses of vaccine and fever therapy.

4 It is hoped that further studies will be made to determine whether a constant relationship exists between Brucellosis and intermittent hydrarthrosis.

Addendum During the past 10 months, the patient's general condition has been unimproved. In spite of large doses of vaccine, a course of neosarsphenamine, and vigorous symptomatic treatment, the temperature continues its nocturnal rise accompanied by drenching sweats. The wrists, ankles and hip joints have become involved with pain and varying degrees of swelling. The knees continue their intermittent hydrarthrosis. The general lymphadenopathy and splenomegaly are the same, but the anemia and weight loss have become more marked. Repeated agglutinations with *Brucella melitensis* remain positive in high dilutions, but cultures of blood and synovial fluid are persistently sterile.

BIBLIOGRAPHY

- 1 SHARPE, J. C., and GROW, M. H. The rheumatic manifestations of undulant fever (To be published.)
- 2 CURTIS, G. M., and KREDEL, F. E. Undulant fever complicating toxic goiter, *Surg. Clin. N. Am.*, 1932, **xii**, 1229-1232.
- 3 BAKER, B. M., JR. Undulant fever presenting clinical syndrome of intermittent hydrarthrosis, *Arch. Int. Med.*, 1929, **xiv**, 128-141.

EDITORIAL

STUDIES ON INSULIN

EVER since its discovery almost fifteen years ago, many attempts have been made to render insulin still more effective as a clinical agent in the treatment of diabetes. These have taken two general directions: one, to find a more convenient and less difficult method of administration, and the other, to enhance its potency and to prolong the period of its physiological action. The chemical nature of this hormone, with its protein-like structure, probably renders it dependent for its physiological effects upon the molecular arrangement of its seven characteristic amino-acids. This structure also makes it vulnerable to attack by the digestive juices, so that it is unlikely that its oral administration in the present form can ever be effective. It has, indeed, been shown repeatedly that the administration of relatively huge doses of insulin by mouth will produce an irregular hypoglycemia. Some of the hormone under such circumstances is probably absorbed before it can be destroyed, but the effects upon the blood sugar are relatively so slight and inconstant as to make this method quite hopeless as a practical measure. The same objections apply to various devices employed to inactivate the digestive juices temporarily, as by alkalization, by ingestion with alcohol, by the use of anti-enzymatic preparations, or by coating the insulin with enzyme resistant materials.

Reports of many efforts directed toward the utilization of other routes of administration may be found in the literature. All eventually have been abandoned because of the uncertainty and lack of precision of the results. The quantity required for any effective action is generally several or many times larger than that required by the subcutaneous route. Rectal applications, insufflation into the naso-pharynx, instillation into the external ear, and even into the conjunctival sac, have been attempted. The writer has recently collected no less than fifteen articles which describe efforts to give insulin by skin incisions. An inconstant effect does seem to be possible with very large doses. A communication has recently appeared reporting promising results by intranasal spray. The history of these studies is always the same. A first enthusiastic report is followed by disappoint-

HILL, D. W., and HOWITT, F. O. *Insulin: its production, purification and physiological action*, London, 1936.

MAJOR, R. H. The intranasal application of insulin, *Jr. Lab. and Clin. Med.*, 1935, **xxi**, 278-280.

CLAUSEN, V., and LOTTRUP, M. C. Experiences with the treatment of diabetes with insulin—epinephrine, *Ugeskr. f. Læger*, 1935, **xcvii**, 747-750.

PRIBRAM, H. Clinical observations on percutaneous insulin action in diabetic patients, *Klin. Wchnschr.*, 1935, **xiv**, 1534.

HEFMANN, S., and KASSOWITZ, H. Experimental foundations of percutaneous insulin action, *Klin. Wchnschr.*, 1935, **xiv**, 1531.

ment as the author discovers the impossibility of obtaining the precision and dependability of action indispensable for clinical use

Nevertheless, the cumbersomeness, inconvenience and pain of the constant hypodermic injections of insulin render any improvement highly desirable. The occurrence of fatty tumors, often disfiguring, as a result of neglect to rotate the site of subcutaneous injections is not so serious a problem as is that of the curious areas of atrophy which are seen from time to time, and which appear to be permanent scars. When one comes to consider the enormous number of hypodermic injections of insulin daily administered by untrained and often careless and dirty individuals, into diabetic tissues which are particularly susceptible to infection, the relative rarity of this complication or of any other is truly remarkable. In the course of ten years a diabetic patient who takes insulin twice daily will receive over seven thousand hypodermic injections.

A more promising line of attack has been that directed toward delaying and enhancing the hypoglycemic action of insulin. If its physiological effect is analogous to that of an enzyme, and current evidence perhaps points in this direction, such investigations may well be considered hopeful and probably eventually fruitful. Injections with various agents which delay absorption by physical means or otherwise have been extensively studied. Mechanical mixture, either of dissolved insulin, or of dry insulin powder, with semi-solid fats or oils, which are themselves absorbed slowly, or with lecithin or cholesterol, or with gum arabic or allied compounds, have not yielded very satisfactory results. Recently Clausen has reported favorable effects with mixtures of adrenalin and insulin. Promising studies upon the enhancement of insulin action by means of combination with protein precipitants, or adsorbents, as metallic salts, particularly those of iron and zinc, have recently been published by Bishoff and Maxwell, and by Scott and Fisher.

Great interest has been aroused in the report of the use of a combination of the protamines derived from the testes of certain species of fish, with insulin hydrochloride, by Hagedorn and his coworkers. These protamines, first extensively studied by Kossel, may form a loose chemical combination with insulin, perhaps analogous to that presented by aniline hydrochloride. The clinical use of this material causes an undoubted prolongation of the usual insulin effect, up to eight or ten hours. The most striking clinical

SCOTT, D. A., and FISHER, A. M. Prolongation of insulin action by protamine and zinc, *Proc. Soc. Biol. Chem.*, 1936, **1**, 448.

KRARUP, N. B. Clinical investigations into the action of protamine insulinate, Copenhagen, 1935.

HAGEDORN, H. C., NORMAN JENSEN, B., KRARUP, N. B., and WODSTRUP, I. Protamine insulinate, *Jr. Am. Med. Assoc.*, 1936, **cvi**, 177.

ROOT, H. F., WHITE, P., MARBLE, A., and STOTZ, E. H. Clinical experience with protamine insulinate, *Jr. Am. Med. Assoc.*, 1936, **cvi**, 180.

HANSEN, P. Enlargement of the liver in diabetes mellitus, *Jr. Am. Med. Assoc.*, 1936, **cvi**, 914.

result so far noted, aside from its influence upon the hyperglycemia and glycosuria, is the reduction of the liver enlargement sometimes observed in cases of poorly regulated diabetes especially in children. Unfortunately, the preparation of the material for injection, and its stability, present certain difficulties and render it impractical for use on an extensive scale in its present form. A flocculent precipitate is formed, and it is necessary to inject this material in an even suspension. The occurrence of insulin reactions is also somewhat disturbing, in the writer's experience. These come on, as a rule, more slowly and insidiously than do those seen with ordinary insulin, so that the danger involved in failure of recognition is possibly greater. Sweating and hunger are much less marked and the occurrence of rather severe headache is quite common.

There is no doubt that further progress along similar lines in order to secure delayed insulin action will now be rapid. It is of interest, as found in determinations of the molecular weight of insulin by the ultracentrifuge method in Svedberg's laboratory, that significant changes occur with variation in the pH value of the solution. Whereas the insulin molecule is relatively stable within the range pH 4.5 to 7.0 (molecular weight about 35,000), outside this range it dissociates into products of smaller size. This dissociation, however, is reversible. It is possible that the greatly enhanced surface area presented by the smaller dissociated particles increases their adsorption on the tissues and hence slows up their physiological utilization, as compared to that of the ordinary insulin molecule. Important developments of practical clinical value in this field may shortly be expected with considerable confidence.

G A H

REVIEWS

Physical Diagnosis By RICHARD C CABOT, M D 11th Edition 540 pages, 16 5
× 23 5 cm Williams and Wilkins, Baltimore 1934

This is the eleventh edition of this deservedly popular textbook. As usual it is notable for the clarity and force with which the material is presented. The well chosen illustrations are a distinct addition to the text. There have been new additions to and enlargements of certain sections, for example those dealing with coronary disease, latent tuberculosis, neoplasms of the lungs and bronchi and the pneumononkioses. The new edition all in all is a further improvement on those preceding it and will no doubt be equally well received.

M C P

Three Philosophers (Lavoisier, Priestley and Cavendish) By W R AYKROYD
227 pages, 13 × 21 cm William Heineman Ltd, London 1935 10/6 net

Historians of medical science often are too concerned with relatively unimportant personal attributes and experiences of the great figures of medicine and too little with their ideas or their contributions. Often too they have more of the bibliophile's interest in the publications that have changed the course of scientific progress than that of the student of science. The present little volume seems to the reviewer a model of its kind. The author writes charmingly of the lives of three great scientists and of the period in which they lived. It is evident that he is thoroughly at home in the history of the late eighteenth century. On this background he develops very clearly and interestingly the story of how each contributed to our present knowledge of the composition of water and air. The significance of Lavoisier's metabolic investigations is well brought out. Toward the end of the volume the later life and death of the three philosophers is well told. To most readers the material especially on the life of Lavoisier will be new. It is a small volume which will be read by any physician with interest and profit.

M C P

Medical Tactics and Logistics By COLONEL GUSTAVUS M BLECH, M C, U S A,
and COLONEL CHARLES LYNCH, M C, U S A, Ret 201 pages, 15 5 × 23 5 cm
Charles C Thomas, Springfield, Ill 1934 Price, \$4 00

The authors have written this book to afford "medical officers, patriotic physicians and medical students a fundamental idea of the nature of their duties in the event of a national emergency." It begins with a number of short chapters on "Theory Development and Principles of War" and then proceeds to recount in considerable detail the military and medical aspects of an imaginary war, or succession of skirmishes about the borders of Maryland and Pennsylvania. All the moves in this conflict are discussed pro and con at some length and a conscientious effort is made to drive home certain elementary lessons. A folder of maps of the region accompanies the volume.

In this war everything proceeded according to regulations. Apparently orders were issued constantly and obeyed promptly, liaison was perfect, everyone knew all he should know about what was going on, maps must have been issued in abundance and medical supplies were never seriously lacking. The behavior of almost everyone was exemplary. The reviewer hopes that the next war will resemble the one here described.

Those who took part as regimental medical officers in the forward areas in the past war will find most of this volume highly theoretical and unreal. However,

there is a foundation of sound doctrine in it, and its perusal will give the battalion surgeon of the future a good general notion of how the medical corps at the front is intended to function. Following this he would do well to read "The Lost Legion" or "Chevrons" to get a more realistic conception of what a war is like.

M C P

Disorders of the Blood By LIONEL E H WHITBY and C J C BRITTON 543 pages, 16 × 24 cm P Blakiston's Son and Co, Inc, Philadelphia 1935

The authors have produced a book which may be recommended unreservedly to the attention of all physicians engaged in the practice of internal medicine. It meets in a very adequate way the need for a monograph in which the large and scattered literature of hematology of the last ten years is gathered together, added to our basic knowledge of the subject and presented as a whole. The earlier chapters deal with the origin, functions and fate of blood cells, the abnormalities of hemopoiesis, and the methods of study and of differentiation of the various formed elements of the blood. Then comes, in several chapters, an excellent discussion of the anemias. The first and second of these chapters deal with the causes of anemia and with the principles of treatment. It would be hard to find elsewhere as compact, as clearly stated and as interesting a discussion of our more recent knowledge of these topics. In the later chapters on the various types of anemia the chapter on pernicious anemia and that on anemias due to disease of the alimentary tract are of particular interest. The anemias of infancy and childhood receive notice in a separate chapter.

The purpuric and hemorrhagic states are discussed rather briefly though even rare forms are mentioned. In the chapter on aplastic diseases the data on agranulocytic angina are derived almost wholly from American sources, and there is very little expression of the authors' own opinions.

The leukemias, affections of the spleen, the blood changes in infection and infectious diseases and in miscellaneous conditions occupy the latter half of the book. Blood groups and blood transfusion are discussed.

The book is well organized and carefully written. There is a good index. References are placed at the end of the chapters. The tables, illustrations and colored plates are helpful.

The treatment of such a large field is necessarily brief, and it is perhaps inevitable that the tone should be at times dogmatic. A more critical evaluation of proposed therapeutic measures would be helpful in some sections. All in all, however, this is a very valuable book. It may be used as a reference or read through with profit as an account of the present status of knowledge concerning disorders of the blood.

M C P

Diseases of the Liver, Gall Bladder, Ducts and Pancreas By SAMUEL WEISS, M D, F A C P 1099 pages, 18 × 26.5 cm Paul B Hoeber, Inc, New York 1935 Price, \$10.00

This large, handsomely printed and illustrated volume is disappointing when put to the test of practical use as a reference volume. It is essentially a compilation of abstracts from the literature. There is a striking lack of orderly and logical sequence in the topical discussions so that the reader is left confused and unsatisfied. Important facts are often stated very briefly or omitted while pages are given to comparatively trivial details. Numerous inaccuracies further detract from the value of the book.

M C P

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the following gifts of publications by members to the College Library

- Dr William C Boeck (Fellow), Los Angeles, Calif—1 reprint,
 - Dr Vincent W Koch (Fellow), Janesville, Wis—1 reprint,
 - Dr M B Marcellus (Fellow), San Francisco, Calif—1 reprint,
 - Dr Walter M Simpson (Fellow), Dayton, Ohio—1 reprint
-

COMMITTEE ON FUTURE POLICY FOR THE DEVELOPMENT OF INTERNAL MEDICINE

Minutes of the Board of Regents, March 6, 1936 "RESOLVED, that a Committee on Future Policy for the Development of Internal Medicine be appointed by the President for the purpose of considering a program of possibilities for using surplus funds for the advancement of Internal Medicine This Committee shall take under consideration all matters outside that of the College Headquarters, such as fellowships, awards, postgraduate education, initiation fees of new Fellows, revolving funds for the aid of research, etc"

The personnel of this Committee, as appointed by the President, Dr Ernest B Bradley, is as follows

James Alex Miller, *Chairman*, New York, N Y
Walter L Bierring, Des Moines, Iowa
Roger I Lee, Boston, Mass
Maurice C Pincoffs, Baltimore, Md
Francis M Pottenger, Monrovia, Calif

Dr George Bachmann (Fellow), Atlanta, Ga, presented a paper on "The Gaseous Metabolism of Glucose, Fructose and a Mixture of These Two Sugars, together with Urinary Findings" at the February meeting of the Dugas Club of the University of Georgia School of Medicine

The Second Annual Postgraduate Course "Neuropsychiatry in General Practice," given by the Staff of the Menninger Clinic, Topeka, Kans, will extend from April 20 to April 25 Dr William C Menninger (Fellow) and Dr Ralph M Fellows (Fellow) are among those contributing to the course

Dr Clayton W Greene (Fellow), Buffalo, N Y, has been appointed a member of the New York Public Health Council by Governor Lehman

Dr George W McCoy (Fellow), of the U S Public Health Service, has been appointed professorial lecturer in preventive medicine at George Washington University School of Medicine

Dr Arthur C Christie (Fellow), Washington, D C, has been reelected President of the Board of Trustees of the American University

Dr Archibald Barklie Coulter (Associate), Washington, D C, has been appointed Director of the Bureau of Tuberculosis of the Health Department of the District of Columbia

Dr Frank R Menne (Fellow), Portland, Ore, and Dr Delbert H Nickson (Fellow), Seattle, Wash, have been elected President and Vice-President respectively, of the recently organized Pacific Northwest Society of Pathologists

Brig Gen Matthew A Delaney (Fellow), Assistant to the Surgeon General U S Army, has retired on his own application. General Delaney graduated from the University of Pennsylvania in 1898. He also held the Certificate of Public Health from Harvard University School of Medicine. He has been in the Medical Corps of the U S Army since 1901, and is retiring at the age of sixty-one. He was White House physician during the administration of President Taft from 1909 to 1913. Earlier he served in the Philippines and during the World War, he was in charge of Base Hospital No 10, and was later detailed as liaison officer with the British War Office. He received the Distinguished Service Medal, and was decorated by the British Government

Dr Joseph C Doane (Fellow), Medical Director of the Jewish Hospital, Philadelphia, and Dr Martha Tracy (Fellow), Dean of the Woman's Medical College of Pennsylvania, have been appointed to the Philadelphia Board of Health, to succeed Dr James M Anders (Master), resigned, and the late Dr Ellwood R Kirby

Dr William B Castle (Fellow), Associate Professor of Medicine at Harvard University Medical School, received the Procter Award on the occasion of "Professional Day" of the Philadelphia College of Pharmacy and Science, January 31

Dr Charles A Doan (Fellow), Professor of Medicine and Director of Research, Ohio State University College of Medicine, Columbus, delivered the Beaumont Lectures for 1936, sponsored by the Wayne County (Mich) Medical Society, March 23 to 24. The lectures were given on "The Histopathology of the Blood"

The Scientific Assembly of the American Medical Association decided in December to have an afternoon session at the coming meeting in Kansas City in May devoted to Tuberculosis, under the Section on Miscellaneous Topics. The officers appointed for this Session were Dr James Alexander Miller (Fellow), New York City, Chairman, Dr Charles Hartwell Cocke (Fellow) Asheville, N C, Secretary. The Session is to be held Wednesday afternoon, May 13, and the preliminary program will include, in addition to the Chairman's Address, papers by Drs Max Pinner, Oneonta, N Y, J Burns Amberson, Jr, New York City, LeRoy S Peters, Albuquerque, New Mex, and J J Singer, St Louis, Mo, all members of the College

ELECTIONS TO FELLOWSHIP

March 1, 1936

<i>Candidates</i>	<i>Sponsors</i>
ALABAMA	
Joseph E. Hirsh, Birmingham	James S. McLester, Charles H. Cocke, Fred W. Wilkerson
ARIZONA	
Benson Bloom, Tucson	Allen K. Krause, Charles W. Mills, W. Warner Watkins
ARKANSAS	
Francis Joseph Scully, Hot Springs	Arthur G. Sullivan, D. C. Lee, Oliver C. Nelson
CALIFORNIA	
Harold Milton Walton, Loma Linda	G. Stirling Landon, Roland Cummings, F. M. Pottenger, James F. Churchill
Clarence Emory Johnson, Long Beach	Samuel M. Alter, Noel F. Shambaugh, F. M. Pottenger, James F. Churchill
Ernest Mosiah Hall, Los Angeles	Roy E. Thomas, Egerton Crispin, F. M. Pottenger, James F. Churchill
Cullen Ward Irish, Los Angeles	John V. Barrow, Samuel D. Ingham, F. M. Pottenger, James F. Churchill
Orlyn Bernard Pratt, Los Angeles	Percy T. Magan, Newton Evans, F. M. Pottenger, James F. Churchill
Harold Guyon Trimble, Oakland	George H. Evans, Chesley Bush, F. M. Pottenger, Hans Lisser
Mark Gerstle, Jr., San Francisco	Dudley W. Bennett, H. Clare Shephardson, Hans Lisser
CONNECTICUT	
W. Bradford Walker, Cornwall	Charles H. Turkington, George Blumer, Henry F. Stoll
Wilmar Mason Allen, Hartford	Otto G. Wiedman, James E. Hutchison, Henry F. Stoll
Wilmot Charles Townsend, Hartford	G. Gardiner Russell, Otto G. Wiedman, Henry F. Stoll
Benedict Richard Harris, New Haven	George Blumer, C. J. Bartlett, Henry F. Stoll
Max Harold Ruby, Waterbury	John H. Foster, J. Harold Root, Henry F. Stoll
DELAWARE	
Joseph Marion Messick, Wilmington	George H. Gehrmann, Olin S. Allen, Lewis B. Flinn
Edgar Raymond Miller, Wilmington	Olin S. Allen, Bartholomew M. Allen, Lewis B. Flinn
MEDICAL CORPS, U. S. ARMY	
Frank R. Borden, Randolph Field, Tex.	Charles R. Reynolds
Thomas Ward Burnett, Salt Lake City, Utah	Charles R. Reynolds
George Clark Dunham, Washington, D. C.	Charles R. Reynolds
George Martin Edwards, Fort Sam Houston, Tex.	Charles R. Reynolds
Robert M. Hardaway, Denver, Colo.	Everett L. Cook, William C. Pollock, Charles R. Reynolds

*Candidates**Sponsors*

Arthur Parker Hitchens, Washington,
D C

Charles R Reynolds

Glenn I Jones, San Rafael, Calif

Charles R Reynolds

John G Knauer, Denver, Colo

Charles R Reynolds

George F Lull, Washington, D C

Charles R Reynolds

Harry D Offutt, Honolulu, T H

Charles R Reynolds

Henry Church Pillsbury, Washington,
D C

Charles R Reynolds

Charles G Sinclair, Fort Sam Houston,
Tex

Charles R Reynolds

MEDICAL CORPS, U S NAVY

John Ryer Poppen, San Pedro, Calif

Perceval S Rossiter

George Washington Taylor, Louisville,
Ky

Oscar O Miller, E R Gernet, Perceval S Rossiter

DISTRICT OF COLUMBIA

Clapham Price King, Washington

William Earl Clark, E Clarence Rice, Wallace M
Yater

ILLINOIS

Thomas J Coogan, Chicago

George W Hall, George H Coleman, Arthur R
Elliott, James G Carr

George B Stericker, Springfield

Cecil M Jack, D O N Lindberg, Samuel E Mun-
son

INDIANA

James Oscar Ritchey, Indianapolis

John A MacDonald, Edgar F Kiser, Robert M
Moore

IOWA

James Stuart McQuiston, Cedar Rapids

Herbert W Rathe, Elmer G Sentz, Walter L
Bierring, Tom B Throckmorton

Benjamin Franklin Wolverton, Cedar
Rapids

John H Peck, Elmer E Kottke, Walter L Bierring,
Tom B Throckmorton

William Edward Ash, Council Bluffs

Ernest Kelley, Aldis A Johnson, Walter L Bierring,
Tom B Throckmorton

John Calvin Parsons, Creston

John H Peck, Daniel J Glomset, Walter L Bierring,
Tom B Throckmorton

Martin Ingeman Olsen, Des Moines

Daniel J Glomset, Addison C Page, Tom B
Throckmorton

Edwin Basom Winnett, Des Moines

John H Peck, Daniel J Glomset, Walter L Bierring,
Tom B Throckmorton

KANSAS

Ralph Mason Fellows, Topeka

William C Menninger, Howard E Marchbanks,
Thomas T Holt

KENTUCKY

Samuel Spafford Ackerly, Louisville

John Walker Moore, William E Gardner, Chauncey
W Dowden

MAINE

Henry Myer Tabachnick, Portland

Eugene H Drake, Elton R Blaisdell, Edwin W
Gehring

*Candidates**Sponsors*

MARYLAND

Paul W Clough, Baltimore

Thomas P Sprunt, George A Harrop, Henry M Thomas, Jr

William S Love, Jr, Baltimore

Thomas P Sprunt, John E Legge, Maurice C Pincoffs, Henry M Thomas, Jr

MASSACHUSETTS

Elmer C Bartels, Boston

Frank N Allan, Lewis M Hursthal, William B Breed

Charles Sidney Burwell, Brookline

Ernest B Bradley, Chester M Jones, James H Means, William B Breed

Roderick Alexander Macaulay, Springfield

Theodore S Bacon, Laurence D Chapin, Roger I Lee, William B Breed

MICHIGAN

Elbert Smith Parmenter, Alpena

Robert H Durham, Frank R Menagh, James D Bruce

Charles E Lemmon, Detroit

Henry R Carstens, Edward D Spalding, James D Bruce

Willard D Mayer, Detroit

Henry R Carstens, Frederick G Buesser, James D Bruce

Lutfi Mustafa Sa'di, Detroit

Frederick G Buesser, Henry R Carstens, James D Bruce

F Janney Smith, Detroit

Frank R Menagh, Robert H Durham, James D Bruce

Franklin Walter Baske, Flint

William H Marshall, Myrton S Chambers, James D Bruce

Roy Herbert Holmes, Muskegon

William M LeFevre, F Herbert Bartlett, James D Bruce

MINNESOTA

Frank Joseph Heck, Rochester

Edgar V Allen, Porter P Vinson, Edward L Tuohy

Charles Hamilton Watkins, Rochester

Arlie R Barnes, Edgar V Allen, Edward L Tuohy

NEW JERSEY

Ferdinand Charles Dingel, East Orange

Joseph W Gardam, Edward C Klein, Jr, Clarence L Andrews

Paolo F Liva, Lyndhurst

Richard E Knapp, Herman Trossbach, Clarence L Andrews

LeRoy W Black, Rutherford

Herman Trossbach, Richard E Knapp, Clarence L Andrews

NEW MEXICO

Carl Herman Gellenthien, Valmora

Meldrum K Wylder, Carl Mulky, LeRoy S Peters

NEW YORK

Ferdinand Michael Jordan, Brooklyn

James F Weir, Mandred W Comfort, Robert A Cooke

Burton L Zohman, Brooklyn

William S Hubbard, Murray B Gordon, Luther F Warren, Robert A Cooke

Harold Francis Robert Brown, Buffalo
J Frederick Painton, BuffaloNelson G Russell, Thomas J Walsh, Allen A Jones
William F Jacobs, Carroll J Roberts, Allen A Jones
Carl Boettiger, George Forbes, Luther F Warren,
Robert A Cooke

Frank R Mazzola, Jamaica

Candidates

Raeburn James Wharton, Johnson City
 Warren F Kahle, Larchmont
 Bernardine Thomas McMahon, Loomis
 Joseph Hajek, New York
 Arthur M Master, New York
 Herman O Mosenthal, New York
 John James Rooney, Rochester
 Earle E Mack, Syracuse
 Stephen Horace Curtis, Troy

Sponsors

Newton Thomas Saxl, Wardner D Ayer, Robert A Cooke
 Arthur F Heyl, Richard A Kern, O H Perry Pepper, Robert A Cooke
 George Foster Herben, J Burns Amberson, Jr, Robert A Cooke
 Walter A Bastedo, Samuel W Lambert, Luther F Warren, Robert A Cooke
 Emanuel Libman, Lewis A Conner, Luther F Warren, Robert A Cooke
 Harlow Brooks, Carl H Greene, Robert A Cooke
 James F Rooney, John J Finigan, Luther F Warren, Robert A Cooke
 Charles D Post, I Harris Levy, Allen A Jones
 Crawford R Green, Howard F Root, Robert A Cooke

NORTH CAROLINA

Stephen Webb Davis, Charlotte
 Paul Allison Yoder, Winston-Salem

Walter O Nisbet, John P Munroe, Charles H Cocke
 Wingate M Johnson, S Douglas Craig, Charles H Cocke

OHIO

George B Topmoeller, Cincinnati
 George Widmer Thorn, Columbus
 Raymond W Bradshaw, Oberlin
 Abel Albert Applebaum, Toledo

Clifford J Straehley, John E Grewe, A B Brower
 Charles A Doan, Roy G Pfozter, A B Brower
 Lewis M Hursthal, Henry J John, Roger I Lee, A B Brower
 Louis A Levison, John T Murphy, A B Brower

PENNSYLVANIA

Elwood Wakefield Stitzel, Altoona
 John Milnes Dyson, Hazelton
 John M Johnston, Pittsburgh
 John Roy Spannuth, Reading
 George McClintock Hutchison, Ridgeway
 Ira A Darling, Warren

E Roland Snader, Jr, Augustus S Kech, E Bosworth McCready
 David Riesman, Joseph C Doane, E J G Beardsley
 Ellis M Frost, Clement R Jones, E Bosworth McCready
 William S Bertolet, Alfred Stengel, O H Perry Pepper, E J G Beardsley
 William G Falconer, E Bosworth McCready
 Wm Egbert Robertson, S Calvin Smith, E J G Beardsley

TENNESSEE

Hugh Francis Crawford, Memphis

Otis S Warr, William Calvert Chaney, J Owsley Manier

TEXAS

Edgar Mullins Dunstan, Dallas
 Caleb Odhelius Terrell, Fort Worth
 Paul Brindley, Galveston
 William Lewis Marr, Jr, Galveston

Henry M Winans, Clarence M Grigsby, Charles T Stone
 May Owen, Will S Horn, Charles T Stone
 Boyd Reading, Titus H Harris, Charles T Stone
 Edward H Schwab, George Herrmann, Charles T Stone

<i>Candidates</i>	<i>Sponsors</i>
Victor Ewald Schulze, San Angelo	Edward H. Schwab, George Herrmann, Charles T. Stone
Paul Maiden Bassel, Temple	George E. Brown (Deceased), Victor M. Longmire, Olin F. Gobel, Charles T. Stone
VIRGINIA	
Edward Lee Alexander, Newport News	Walter B. Martin, C. Lydon Hurrell, J. Morrison Hutcheson
WASHINGTON	
Clyde Reynolds Jensen, Seattle	James E. Hunter, John M. Blackford, Charles E. Watts
WEST VIRGINIA	
George Holt Barksdale, Charleston	Walter E. Vest, Arthur A. Shawkey, John N. Simpson
WISCONSIN	
Vincent William Koch, Janesville	Joseph S. Evans, William S. Middleton, Rock Slevster
Harold M. Coon, Stevens Point	Joseph S. Evans, William S. Middleton, Rock Slevster
CANAL ZONE	
Ernst Thonard-Neumann, Cristobal	Lewis B. Bates, Tomis G. Guardia, William M. James
HAWAII	
Arthur W. Duryea, Honolulu	Harry L. Arnold, Adolph G. Schuack, James Alex. Miller
PUERTO RICO	
Juan Antonio Pons, Floral Park, Rio Piedras	Miguel Roses Artau, Ramon M. Suarez
Oscar Costa-Mandry, San Juan	Miguel Roses Artau, Ramon M. Suarez
Rafael Rodriguez-Molina, San Juan	Miguel Roses Artau, Ramon M. Suarez

ELECTIONS TO ASSOCIATESHIP

March 1, 1936

<i>Candidates</i>	<i>Sponsors</i>
ALABAMA	
William Wallace Alexander, Florence	Harry M. Simpson, James S. McLester, Fred W. Wilkerson
ARKANSAS	
Lorenzo Dow Massey, Osceola	Otis S. Warr, James B. McElroy, Oliver C. Melson
CONNECTICUT	
Walls Willard Bunnell, Farmington	John A. Wentworth, James E. Hutchison, Henry F. Stoll
Frederick Erwin Tracy, Middletown	Henry O. Colomb, George Blumer, Henry F. Stoll
Theodore George Klumpp, New Haven	Francis G. Blake, Willard B. Soper, Henry F. Stoll

*Candidates**Sponsors*

MEDICAL CORPS, U S ARMY

Elias Earle Cooley, Washington, D C	Charles R Reynolds
John Dibble, Carlisle, Pa	Charles R Reynolds
George C H Franklin, Fort Leavenworth, Kan	Charles R Reynolds
Leon Lloyd Gardner Washington, D C	Charles R Reynolds
Don Longfellow, Washington, D C	Charles R Reynolds
Alfred Mordecai, Schofield Barracks, T H	Charles R Reynolds
Paul Adolph Schule, San Francisco, Calif	Charles R Reynolds
Seymour Crandall Schwartz, El Paso, Tex	Charles R Reynolds
Robert E Thomas, Winthrop, Mass	John T Aydelotte, George F Aycock, Charles R Reynolds
Frank Wiley Wilson, Washington, D C	Charles R Reynolds

DISTRICT OF COLUMBIA

Isidore Lattman, Washington	Tomas Cajigas, Arthur C Christie, Wallace M Yater
Charles Hamilton Wolohon, Takoma Park, Washington	Percy T Magan, George T Harding, III, William Gerry Morgan Wallace M Yater

GEORGIA

Abner Wellborn Calhoun, Atlanta	H Cliff Sauls, John Baker Fitts, Glenville Giddings
---------------------------------	---

ILLINOIS

Jacob S Golden, Chicago	Frederick Tice, Arthur E Mahle, James G Carr
William Samuel Hoffman, Chicago	Hugh A McGuigan, Arthur E Mahle, James G Carr
Perry Julius Melnick, Decatur	Cecil M Jack, D O N Lindberg, Samuel E Munson
Milton E Rose, Decatur	Cecil M Jack, Otis O Stanley, Samuel E Munson
Dean Field Stanley, Decatur	Otis O Stanley, Cecil M Jack, Samuel E Munson
Harold C Lueth, Evanston	Nathan S Davis, III, Andrew C Ivy, James G Carr
Villairs Thomas Austin, Urbana	Arlie R Barnes, Harry L Smith, Edward L Tuohy

INDIANA

John Willard Ferree, Bluffton	James G Carr, Arthur E Mahle, Robert M Moore
-------------------------------	--

IOWA

Albert Andrew Schultz, Fort Dodge	Lee R Woodward, Aldis A Johnson, Tom B Throckmorton
-----------------------------------	---

KENTUCKY

Morris M Weiss, Louisville	Emmet F Horine, Morris Flexner, Chauncey W Dowden
----------------------------	---

MARYLAND

James Givings Arnold, Jr, Baltimore	Thomas P Sprunt, Louis Krause, Maurice C Pincoffs, Henry M Thomas, Jr
-------------------------------------	---

Candidates

Alan Bernstein, Baltimore
 Edwin Bosley Jarrett, Baltimore
 Samuel Whitehouse, Baltimore
 Walter LaFollette Winkenwerder, Baltimore

Sponsors

Louis P. Hamburger, Sydney R. Miller, Henry M. Thomas, Jr.
 Walter A. Bretjer, Sydney R. Miller, Henry M. Thomas, Jr.
 Thomas P. Sprunt, Charles W. Wainwright, Henry M. Thomas, Jr.
 Thomas P. Sprunt, George A. Harrop, Henry M. Thomas, Jr.

MASSACHUSETTS

Richard James Clark, Boston
 James Addison Halsted, Dedham
 Robert Battaile Hiden, Stockbridge
 Frank Benjamin Carr, Worcester

Donald S. King, Chester M. Jones, James H. Means, William B. Breed
 Walter Bauer, Chester M. Jones, William B. Breed
 Paul Dudley White, Chester M. Jones, James H. Means, William B. Breed
 George M. Albee, John J. Dumphy, Roger I. Lee, William B. Breed

MICHIGAN

Walter M. Bartlett, Benton Harbor
 Louis John Bailey, Detroit

Russell L. Cecil, Fritz B. Talbot, James D. Bruce
 William J. Stapleton, Jr., John L. Chester, James D. Bruce

Robert Berman, Detroit

Samuel S. Altshuler, Henry R. Carstens, James D. Bruce

Daniel P. Foster, Detroit

Frank R. Menagh, Robert H. Durham, Charles G. Jennings (Deceased), James D. Bruce

Nicola Gigante, Detroit

Henry R. Carstens, Edward D. Spalding, James D. Bruce

Ezra Lipkin, Detroit

William H. Gordon, Hugo A. Freund, James D. Bruce

William Lyon Lowrie, Jr., Detroit

Frank R. Menagh, Robert H. Durham, James D. Bruce

Clarke M. McColl, Detroit

Frank J. Sladen, Robert H. Durham, James D. Bruce

Solomon George Meyers, Detroit

Henry R. Carstens, Edward D. Spalding, James D. Bruce

Gordon B. Myers, Detroit

Edward D. Spalding, Henry R. Carstens, James D. Bruce

Clarence E. Reynier, Detroit

Frank R. Menagh, John G. Mateer, James D. Bruce

Saul Rosenzweig, Detroit

William H. Gordon, Douglas Donald, James D. Bruce

George C. Thosteson, Detroit

Frederick G. Buesser, Henry R. Carstens, James D. Bruce

Russell Sherwood Anderson, Howell

George A. Sherman, Stuart Pritchard, James D. Bruce

MINNESOTA

Alexander Edward Brown, Rochester

David M. Berkman, Edward G. Bannick, Edward L. Tuohy

John Francis Briggs, St. Paul

Gordon R. Kamman, Edward J. Engberg, Edward L. Tuohy

NEW HAMPSHIRE

Charles Henry Parsons, Concord

Henry A. Christian, Fred E. Clow, Robert B. Kerr

*Candidates**Sponsors*

NEW YORK

Herbert J Ulrich, Buffalo
 John Ludwig Hoffman, Kenmore
 N Stanley Lincoln, Mount Morris
 Herbert R Edwards, New York
 Oswald R Jones, New York
 Robert M Lintz, New York
 Charles Aden Poindester, New York
 Aleksei A Leonidoff, Poughkeepsie
 John N Haycs, Saranac Lake
 Ellery George Allen, Syracuse
 Louis Max Hickernell, Syracuse
 J Winthrop Pennock, Syracuse
 Jesse Randolph Pawling, Watertown

Abel Levitt, William F Jacobs, Allen A Jones
 Nelson G Russell, Clayton W Greene, Allen A Jones
 Max Pinnocr, J Burns Amberson, Jr, Allen A Jones
 John K Deegan, Willard B Soper, Luther F Warren, Robert A Cooke
 Edward P Eglee, J Burns Amberson, Jr, Robert A Cooke
 Joseph Lintz, Willard H Squires, Robert A Cooke
 Irving S Wright, A Wilbur Duryee, Robert A Cooke
 C Knight Deyo, Scott Lord Smith, Luther F Warren, Robert A Cooke
 Lawrason Brown, Edward P Eglee, Allen A Jones, Robert A Cooke
 Edward C Reifenstein, Maynard E Holmes, Robert A Cooke
 Maynard E Holmes, William J McNeerney, Allen A Jones
 Maynard E Holmes, Wardner D Ayer, Allen A Jones
 Walter Fox Smith, William Wallace Hall, Allen A Jones

NORTH CAROLINA

Kilby Pairo Turrentine, Kinston
 Arthur Thomas Wyatt, Lillington

Paul F Whitaker, William B Kinlaw, Charles H Cocke
 William T Rainey, Paul P McCain, Charles H Cocke

OHIO

Theodore Liston Bliss, Akron
 Irving H Schroth, Cincinnati
 Charles Spencer Higley, Cleveland
 Frank McLeod Wiseley, Findlay

George E Brown (Deceased), Edward H Rynearson, A B Brower
 Jacob L Tuechter, David A Tucker, Jr, A B Brower
 Charles T Way, Joseph C Placak, A B Brower
 Willard C Stoner, William H Gordon, A B Brower

OKLAHOMA

Elmer R Musick, Oklahoma City
 Franklin Jesse Nelson, Tulsa

Wann Langston, John E Heatley, Lea A Riely
 Russell C Pigford, C J Fishman, Lea A Riely

PENNSYLVANIA

Joseph Warren Hundley, Jr, Philadelphia
 Edgar Lorenz Dimmick, Scranton

James E Talley, Joseph T Beardwood, Jr, George Morris Piersol
 William M Donovan, Arthur E Davis, E J G Beardslev

SOUTH CAROLINA

Olin Burnham Chamberlain, Charleston
 Gustave Patrick Richards, Charleston

Francis B Johnson, Joseph H Cannon, Robert Wilson
 Francis B Johnson, Kenneth M Lynch, Robert Wilson

*Candidates**Sponsors*

SOUTH DAKOTA

Donald Luther Kegaries, Rapid City

George E. Brown (Deceased), Nelson W. Barker,
Julius O. Arnson

TEXAS

Henry Napoleon Gemoets, Houston

Alvis E. Greer, James H. Agnew, Charles T. Stone

VERMONT

Ellsworth Lyman Amidon, Burlington

Paul K. French, David A. Cooper, Clarence H.
Beecher

WASHINGTON

Harry Joseph Friedman, Seattle

George C. Miller, John M. Blackford, Charles E.
Watts

Trecy Henry Duefeldt, Tacoma

Lester J. Palmer, George C. Miller, Charles E.
Watts

WEST VIRGINIA

Paul H. Revelcomb, Charleston

Arthur A. Shawkey, Charles A. Way, John N.
Simpson

PUERTO RICO

Guillermo S. Marques, Arecibo

Miguel Roses Artau, William B. Porter, Ramon M.
Suarez

Cesar Dominguez, Hamacrio

Miguel Roses Artau, William B. Porter, Ramon M.
Suarez

Manuel de la Pila Iglesias, Ponce

Miguel Roses Artau, William B. Porter, Ramon M.
Suarez

Jose Landron, San Juan

Miguel Roses Artau, William B. Porter, Ramon M.
Suarez

Antonio Ortiz y Ortiz, San Juan

Miguel Roses Artau, William B. Porter, Ramon M.
SuarezCarlos Eduardo Munoz MacCormick,
SanturceMiguel Roses Artau, William B. Porter, Ramon M.
Suarez

CENTRAL AMERICA

El Salvador

Raul Arguello, San Salvador

Thomas G. Guardia, Cornelius D. Briscoe, William
M. James

ANNALS OF INTERNAL MEDICINE

VOLUME 9

MAY, 1936

NUMBER 11

THE RÔLE OF EMOTION IN DISEASE *

By WALTER B. CANNON, *Boston, Massachusetts*

WHEN your President asked me for the title of the address for this evening, I had in mind some ideas which I wished to elaborate and which could be included under the heading, "The rôle of emotion in disease." The title is so comprehensive, however, that I must set definite limits to the parts of the subject to be considered. This can be done by use of a method time-honored in the history of medicine—the statement and exposition of aphorisms. There are ten of them.

1 *In modern life infections have diminished and nervous strains have increased.* Anyone whose years allow him to survey the events of the last third of a century is aware of profound changes in the conditions of our existence. Among them is a remarkable shift in the importance of common types of illness. Diseases formerly regarded as plagues and pestilences are now largely under control or have almost disappeared. Tuberculosis is no longer "master of the kings of death", diphtheria has lost most of its terrifying character, the mortality in measles and scarlet fever has gradually been reduced to about a third that of a generation ago, and typhoid and yellow fever, once our arch enemies, may now be regarded as conquered. Release from these and other similar scourges is rightly counted among the great blessings which medicine has conferred upon mankind.

At the same time with these liberations from damaging and death-dealing infections, however, new and strange circumstances have developed in which men and women must conduct their lives. The ox-cart, the horse and buggy and the bicycle, bad losers in the race for speed, have been crowded out by the motor car. The cry for faster and faster travel has been answered by engines which now permit us to rush along the highways at 50, 60 or 70 miles an hour. Tens of thousands killed annually, and hundreds of thousands injured, measure the consequent jeopardy of life and limb. The meanings of these figures in the distress and remorse of the surviving drivers and their victims, in the pains of the crippled, and in the anguish of inconsolable loss among those who look upon their dead, are wholly immeasurable.

* Convocational Oration, Sessions of American College of Physicians, Detroit, March 4, 1936.

From the Laboratory of Physiology, Harvard Medical School.

Accompanying the development of the automobile has been an extraordinary change in the occupation of our people. From a population 60 per cent rural in 1900, we have turned into a population 60 per cent urban. The cities have gained over the farms more than 30 million inhabitants. Whatever its hazards, life in the country has admirable liberty, independence and opportunity for self-direction. Those who have chosen to live in the great cities are often confined to a routine of fixed hours and monotonous tasks. Many lead a sedentary existence, which breaks sharply the age-long racial habit of using the big muscles of the body for gaining sustenance, and the muscles, instead of keeping the body fit, become flabby and inefficient. Furthermore, as hired bookkeepers, clerks and accountants, or as hands in foundries and factories, city dwellers become entangled in the great web of dependency. Specialized work implies limited freedom. The defects of the present commercial and industrial system are not revealed so long as it operates smoothly. It is when a strike among glass molders, for example, stops tens of thousands of other workmen, or the overwhelming of an employer adds the host of his laborers to the masses of the unemployed, that helpless dependence becomes obvious. No wonder that bitter experience can lead to worry and anxiety and to fits of dark depression, and that wives and children must share the gloomy chances with the men who face the tragedy of the lost job. And illness, when it comes, adds its weight to the feeling that support is insecure.

Although reliable statistics are hard to obtain, it would appear that the intense drive and pressure of the new life, its worries and its dreads, place a strain upon men and women which often is too great to be borne. The suicide rate went steadily upward during the recent years of excitement and depression until, in 1932, in the United States it was over 50 per cent higher than during the five years after the War. That rise meant an increase of more than 6000 suicides in 1932 alone. Among diseases suggesting strain are those of the heart and blood vessels, which have nearly trebled in the last three decades. Angina pectoris, emotionally stirred if not emotionally started, now has in New York and Massachusetts three times the number of victims it had in 1900. In New York exophthalmic goiter—that picture of persistent fright—has consistently increased as a cause of death until it has doubled what it was between 1906 and 1910. But these are *mortality* figures, and as such are only indicative of the point which I wish to make. That point is that since the turn of the century an important change in the phenomena of disease has occurred—the seriousness of infection has been undergoing a remarkable decline, and strains and stresses, especially affecting the nervous system, have been on the increase. The disorders resulting therefrom may not lead directly to death and thereby affect statistics, but nevertheless they may cause an immense amount of distress and pain, both directly in the patient himself and indirectly in those bound close by family ties. I refer to the disorders due to emotional causes, fears, resentments and frustrations.

2 *The medical profession has not recognized in a practical way the recent shift in the etiology of disease* Contemporaneous with the changes which we have just reviewed there has been a development of "healing cults" in our country to a degree not seen in other lands. Persons who have had no discipline whatever in the medical sciences, and no rigorous clinical experience, have been recognized by the public, and to some degree by members of our profession, as capable of undertaking the treatment of the sick. Prominent among these cults are Christian Science and other systems of mental healing. I would add also Freudian methods as practiced by laymen, for Freud himself has argued vigorously in favor of the application of his ideas by psychologists and others who have had no medical training. The Christian Scientists deny the existence of bodily disease altogether and account for so-called illness as being the result of mental error. For the more metaphysical Freudians, likewise, the brain and its modes of government of the organism seem to be quite negligible, the id, the ego, the superego and the censor, and occasional unfortunate family quarrels among these ghostly figures, suffice to explain many of the troubles of existence.

How may this purely mentalistic attitude toward disease be interpreted? The explanation, no doubt, is complex. Fundamentally, I believe, it results from our failure to recognize the considerable rôle which emotional factors have come to play in the onset of illness, especially among people who are harassed by novel and severe demands on their nervous capacities. The medical curriculum has paid relatively little attention to this important matter. In the teaching of medical students emphasis has been laid on disease as it is manifest at the autopsy table or under the microscope. Bacterial agents, poisons, and physical trauma have been recognized as the obvious common causes of disability. In their application, through decades these notions of pathology have, to be sure, proved their worth. The immense and admirable advances of both curative and preventive medicine during the last four-score of years are properly attributed to them. But perhaps the insistence on morphological pathology and the routine attention to physical signs have led to a belittling and depreciation of human disorders so subtle that they leave no obvious trace.

Is it not true that the recent almost revolutionary transformation of the conditions of life has altered the relative importance of etiological factors? Since bacterial agencies have become less potent, and disturbances of nervous functions have become a greater liability, should not we recognize the change? It will not be easy. Fears and worries, persistent hatred and resentment—what pathology have they? Are they not manifestations of the psyche? And who knows about the psyche? Taught to deal with concrete and demonstrable bodily changes, we are likely to minimize or neglect the influence of an emotional upset, or to call the patient who complains of it "neurotic," perhaps tell him to "go home and forget it," and then be indifferent to the consequences. But emotional upsets have concrete and

demonstrable effects in the organism. It is not to be wondered at, therefore, that when a patient in trouble appeals to us for aid and finds us lacking in sympathy and interest, he turns to faith healers, or Christian Scientists, or psychoanalysts, whether they be expert or not, seeking the help which he needs.

3 *A consideration of the physiological aspects of emotional disturbance discloses a way toward understanding it.* Patients suffering from emotional strain offer to the conventionally trained physician a dilemma, he cannot put his finger on any observable lesion that would yield insight into their troubles, nor can he use his routine methods to explore that complex and mysterious realm where the strain seems to have its center. An escape from this dilemma, which avoids both the demand for palpable evidence of disease and also the vagueness and mysticism of the psychological healers, can be found, I believe, in an examination of the physiological processes which accompany profound emotional experience. As a physiologist I have good reason to regard the movement of nerve impulses along the invisible pathways of the brain as being no more associated with any permanent structural change than one would find, after I cease speaking, in the neurones which now innervate the muscles of my larynx. Yet, in the minute and intricate net of microscopic threads in the cerebral cortex, easy courses may become established which may lead to personal disaster—which may, indeed, result in conduct so intolerable that society will take away from the individual his free action. The habitual pickpocket, the incorrigible forger, the persistent incendiary are persons who exhibit such inwrought and established antisocial behavior. One would look in vain for the pathology of their neurones, yet we must admit that their repeated crimes result from repetition of the same occurrences in their brains. And similarly when typical visceral disturbances occur in regular consequence of emotional excitement—just such disturbances as can be induced by stimulating the visceral nerves—as a physiologist I have good reason to regard them as resulting from discharge of nerve impulses due to the excitement. I propose, therefore, that we try to keep out of the foggy realm of metaphysical medicine and consider emotions from the physiological point of view. Although I shall use words which designate subjective states, such as “fear,” “rage” and others, let it be understood that I use them only as convenient abbreviations for activities in the nervous system. Throughout the discussion I shall be concerned with the *physiological* aspects of affective disturbances—that is, with the nervous mechanisms which are involved. Admittedly I am laying little emphasis on the subjective states, the glow of color and warmth, or the darkness of doomsday, with which emotional states may surround simple perceptions or purely intellectual processes. Such states I do not wish to “physiologize.” Let us for the present attend to the *expressive* aspect, the “motion” part of the emotion.

From the physiological point of view an emotion is a typical reaction pattern, having in its *expressive* features characteristic facial and postural

attitudes Only a glance is needed to tell the disposition of a lost child sobbing for his mother, or a young tough who with clenched fist and gritted teeth seeks his enemy, or a thief in wild-eyed flight from an armed policeman Expressions of grief and rage and fear are ingrained in cerebral structure Just as sneezing and coughing are reflexes, provided in the congenital organization of the nervous system, so likewise is emotional behavior One does not have to take lessons in ways of showing one's feelings Place a man in danger and he is afraid, interfere with him as he satisfies some natural instinct and he becomes angered When the appropriate stimulus is applied there is commonly a prompt response So uniform is the response that among different peoples, and even in lower animals, its meaning is understood without explanation, and so persistent is it throughout life that an old man's expression of grief resembles that of a child In practically all respects the reactions of the body to emotion-provoking situations have the characteristics of simple reflexes

4 *Profound emotional disturbances are expressed in effects on viscera which are innervated by the autonomic nervous system, and especially by the sympathetic division of that system* If an emotional reaction is intense, visceral disturbances may occur which involve the entire organism The movements of the gastrointestinal tract are stopped, the digestive secretions are inhibited, the heart is made to beat more rapidly, the blood pressure is elevated by vasoconstriction in the skin and the splanchnic area the spleen is contracted so that its content of concentrated corpuscles is squeezed out, the adrenal medulla is made to secrete adrenine, blood sugar is increased by discharge from the liver, and sweat may be poured out on the body surface All these extensive alterations in the organism are displays of the functioning of the sympathetic division of the autonomic nervous system, whose outreaching filaments are distributed to every region of the body, from the hairs on the top of the head to the glands on the soles of the feet

There is evidence, also, that intense fear, for example, may involve in addition the parasympathetic control This effect seems to be more manifest in the activities of the sacral division than in those of the cranial Emptying of the bladder and rectum and cases of emotional diarrhea at times of excitement belong to this group of responses

Though there are instances of dominance of the sacral visceral nerves in emotionally disturbing conditions, the typical and more usual effects are those induced by the sympathetic Simultaneously with the discharge of sympathetic impulses, as already noted, the adrenal medulla is made to secrete Since the product, adrenine, cooperates with and reinforces sympathetic nerve impulses, we may say that a sympatho-adrenal system provides the means by which, as a rule, emotional states affect the organism

5 *Emotional stimulation of the sympatho-adrenal system is useful for immediate physical struggle, but otherwise may be deeply disturbing* The overlapping and interlacing of the preganglionic fibers as they reach up and down the lateral chains of sympathetic ganglia indicate an arrangement for

extensive discharge of nerve impulses throughout the body. The distribution of cooperative adrenine in the blood stream, which is general and indeterminate, supports the view that normally the sympatho-adrenal organization is such as to allow it to work as a whole. When there is intense excitement, that is what happens, the entire organism, as previously mentioned, may be brought under sympatho-adrenal influence, and all the bodily forces mobilized for action. It is noteworthy that the changes wrought under these conditions closely parallel the changes which occur in vigorous muscular effort. Indeed, when we consider the age-long racial association of fear with the impulse to run away or escape, and of anger with the impulse to attack, these bodily changes at critical moments may reasonably be interpreted, as I have detailed elsewhere,¹ as preparations for struggle, perhaps a supreme struggle, for existence.

There is another fundamental function of the sympatho-adrenal system, however, which is related to its emergency function and which must be regarded. That is its service in preserving constant conditions, or homeostasis, in our body fluids, the blood and lymph.² Such constancy makes possible for us uniform and consistent performance of our physiological processes. Does the temperature tend to fall and make all our motions slow? The sympathetic constricts blood vessels and increases heat production by discharging adrenine. Does the temperature tend to rise and imperil the integrity of the brain? The sympathetic relaxes surface arteries and pours out sweat for cooling. Is there danger of too little sugar in the blood, with possible convulsions and coma? The sympatho-adrenal agency steps in and liberates a supply of glucose from the hepatic stores and prevents disaster. Does vigorous muscular effort produce non-volatile acid which might overwhelm the alkaline buffer in the blood and stop all action? The sympathetic quickens the pumping of the heart, raises the general blood pressure, makes the blood flow faster through the laboring muscles, unloads extra corpuscles from the spleen, and by thus greatly augmenting the supply of oxygen in the needy parts, permits the non-volatile acid to be burned to innocuous volatile carbon dioxide and the peril is escaped.

The bodily changes in emotional excitement may be considered as anticipatory of many of these dangers. The forces of the organism are put upon a war-footing. But if there is no war to be waged, if the emotion has its natural mobilizing effects on the viscera when there is nothing to be done, obviously the very system which functions to preserve constancy of conditions within us is then employed to upset that constancy. It is not surprising, therefore, that fear and worry and hate can lead to harmful and profoundly disturbing consequences.

6 *The sympatho-adrenal system, though organized for diffuse and widespread action, may influence excessively separate organs or functions.* The evidence for this statement is derived, not from experimental data, but from clinical testimony. To what degree separate organs or functions may be influenced without attendant implication of the rest of the sympathetic has

not been determined. I suggest that here lies an interesting field for research. The indications from case reports point to the possibility that an intense emotional shock, or prolonged emotional strain, may result in one or another of the viscera becoming so subject to sympathetic impulses that even slight perturbations in the daily routine will have noteworthy effects.

Among such conditions may be noted a sensitive reaction of the heart, seen occasionally in soldiers who have been exposed to the terrors of warfare, the slightest excitement sends the pulse bounding up to 140 or 150 beats per minute. Or the vasoconstrictor center is so sensitive that the blood pressure jumps up 40 or 50 millimeters whenever an unhappy event is mentioned. Emotional "dyspepsia" so-called, including disturbances of gastric secretion and motility, due to worry or anger, spasm of the cardiac and pyloric sphincters, readily understandable because both sphincters are tightened by sympathetic impulses, vaginismus, also explained by sympathetic innervation of the encircling smooth muscle—all these are pertinent instances. Perhaps most noteworthy are cases of exophthalmic goiter, in which the striking appearance of the patient is that of chronic fright. The rapid heart, the sweating palms and the bulging eyes all tell a tale of increased activity of at least the upper portion of the sympathetic system. Friedgood's recent studies³ in the Harvard Physiological Laboratory suggest that sympathetic impulses may act primarily on the anterior lobe of the pituitary and that thyroid involvement is secondary to that. Whatever may be the way in which the disease is evolved, the evidence seems to me overwhelming that a large proportion of the cases have an emotional origin.

7 *The neural basis for emotional expression is organized in the thalamic region of the brain.* The close resemblance between emotional expressions and simple reflexes has already been emphasized. It is characteristic of simple reflexes that they have their centers in the spinal cord or in the part of the brain which is racially most ancient, the primitive brain stem. We have ample evidence to prove that the neurone patterns for the full display of the elementary emotions are organized in this part of the cerebrum. As Bard⁴ has shown, the decorticate cat, without any cerebral hemispheres, will snarl and bite when pinched, will crouch and run away when stimulated by a hissing or a loud noise, and will display characteristic mating behavior when appropriately stimulated. Here are the typical signs of rage, fear and sexual excitement, exhibited after the cerebral cortex, which associates the organism with the outer world, has been wholly removed. Characteristically the emotional expression of decorticate animals is extreme. When rage—what we called "sham rage"—occurs in such a truncated creature, the sympatho-adrenal system is supremely active, the heart rate may double, blood sugar may increase five-fold, blood pressure is markedly elevated, sweat is poured out on the toe pads, and the hair stands erect from head to tail tip. Because the display of typical emotional responses after decortication tends to be superlative, the inference is obvious that the cortex normally exerts an in-

hibitory influence on the lower centers. Decortication lifts the check and permits the display to have unlimited intensity.

The neural organization demonstrated in lower animals is present also in man. A unilateral tumor in the thalamic region—i. e., at the emotional level—may not alter a voluntary laugh or a voluntary grimace of pain, originated in the cortex. A real laugh or grimace, however, induced by proper affective stimuli, is unilateral. Or a patient with features distorted by one-sided palsy will, when he laughs or weeps because of true feeling, express his attitude with both sides of his face. In short, the muscles of expression are governed from two levels—the cortical level in the cerebral hemispheres, and the emotional level in the diencephalon.

Quite in accord with this evidence are the emotional manifestations in man when he is chemically decorticated. The primary stage of ether anesthesia, and subjection to nitrous oxide, illustrate that condition. Under ether the patient may put up a vigorous fight, and under nitrous oxide he may laugh or weep. In the circumstances voluntary or cortical government has been abolished, but the features of rage or pleasure or grief are still patterned in the emotional level.

Although there is evidence that artificial stimulation of certain parts of the cortex can influence some internal organs, the physiological significance of this fact is still unknown. We do know that as a rule we cannot directly either start or stop the motions of the stomach, for example, or the acceleration of the heart or an extra output of sugar from the liver. Thus, although cortical government may prevail over that part of emotional expression that is seen in features and posture, it is impotent in checking the effects on the viscera. A man apparently calm may be "boiling" inside.

8 *The nervous system is organized in two grand divisions operating outwardly and inwardly.* The universal distribution of the fine nervous filaments to well-nigh every minute area within us need not be emphasized. Stimulation of any point on the skin may send reverberations throughout the whole organism. By means of this intricate and elaborate net of communicating fibers the multitudes of individual parts of the body are unified and made to cooperate.

In the central organization of the nervous system two main divisions may be distinguished. There is what I have called the *exteroffective* division, that which by means of sensory receptors is impressed by changes in the outer world and which by means of striated muscles and bony levers works outwardly to change our surroundings and our relation to them. Apart from simple reflexes this division is normally managed from the cerebral cortex. It is related to the external environment, both material and social, in a prodigious complex of impressions, memories, habitual reactions and new adjustments. Through words and pictures, as symbols for objects and acts, the exteroffective division may become a part of an indefinitely extensive universe. And then there is the *interoffective* division. This is the individual, personal division. It is the autonomic or involuntary system,

already detailed. It works inwardly and affects the muscles and glands of the viscera. It is primarily concerned with the internal environment, the fluid matrix of the body, and, as already noted, normally serves to maintain constancy, or homeostasis, in the watery surroundings of the living parts, inside our dermal envelope. Tendencies toward change—toward hyperthermia or hypothermia, hypoglycemia or acidosis—promptly bring this division into corrective service. In natural circumstances it works cooperatively with the exteroceptive division, keeping the conditions of the fluid matrix fit for continued activity of that division. But the interoceptive division is governed at the emotional level. Again, in natural circumstances, this division, under emotional control, cooperates with the exteroceptive division.

9 *The cerebral cortex serves to interpret the nature of outer objects and to direct emotional forces when these are liberated.* The classical experiments of Pavlov have shown that by means of its agents, the receptors on the body surface, the cerebral cortex analyzes the external environment and brings outer objects into use by the organism. Thus these objects acquire new meaning. A flash of light or the ring of a bell is quite an indifferent stimulus until, for example, it becomes associated with feeding, whereupon it acquires efficacy and is known as a conditioned stimulus. Then the flash or the ring will start the saliva flowing, an effect beyond voluntary control, in the parasympathetic realm. Experiments on man have proved that stimuli can be similarly conditioned which will cause responses, such as narrowing of the pupil and vasoconstriction—again responses beyond voluntary control, and now in the realm of sympathetic innervation. It is evident that, although the viscera are ordinarily not under direct cortical (i.e., voluntary) influence, the natural reflex response can be extended by relating an ineffective with the effective stimulus. In similar manner indifferent objects may be made into effective stimuli for emotional reactions. The banging of a door renews all the horror of a shell-burst and sends the sensitized war-victim into pitiable fright—the noise is only incidental. A visit to a grave brings back acutely the pangs of grief—the grave as such is a bit of elevated earth.

It is by associations, acquired in experience or through verbal symbols, that objects become emotion-provoking. In this category are *words*, words which have been colored by feeling. We have all heard of "fighting words," those derogatory terms which, when earnestly applied to a man, bring anger on the instant. There are also scare-words which, when carelessly applied to a patient, make him anxious and apprehensive. "Your arteries are twisted," "your heart is rather small," or "a little enlarged," "your stomach has sagged," "your blood pressure is high"—these are examples. And then there are comfort-words, expressions which, coming from a trusted physician, banish fear. By use of these symbols the nervous system can be played upon as though an instrument. The charlatan employs

them to establish conditions which he can capitalize for his own profit. The wise doctor knows how to use them as a part of his therapy.

Experimental tests show that emotion-provoking associations of objects and symbols are established in the cerebral cortex. To the decorticate dog the brandished stick is not a menace—it has no meaning. And to the intact dog the stick may mean danger or may mean play, dependent on the way it is used. If in the woods we encounter a bear we shall not be afraid on noting that it is a stuffed bear. We may be very much afraid if it proves to be a live bear and advancing toward us. The total situation is interpreted by cortical processes, and in accord with the interpretation the emotional level discharges into the viscera or not.

If the viscera are roused and the body is prepared for struggle, the cortex once more serves an interpretative function. It directs the response. Bard's decorticate cats, if stimulated by being pinched, showed signs of anger, but they did not react by biting the experimenter, instead they commonly bit their own bodies.⁴ Or consider fear of the bear in the woods. Fear is attended by the impulse to escape from danger. But how? Is it better to run or better to climb a tree? Again, in accord with the total situation, cortical operations determine the course to pursue.

10 *The nervous system, the specialized system for integration of the body, is so organized that it may itself disintegrate.* As a rule, when there is a possible antagonism between actions, the nervous controls operate in such a way that the opposed actions are made reciprocal. Thus when we contract the biceps, automatically the antagonistic triceps muscle is relaxed. This mutual adjustment is found universally in the functioning of skeletal muscles which are set to work one against another, and also in smooth muscles which are similarly arranged.

There is a part of the nervous system, however, in which these nice reciprocations may not prevail. That is where the two grand divisions of the system—the exteroceptive and the interoceptive—may come into conflict. We have already noted the evidence that the cerebral cortex, governing the exteroceptive system, exercises a check on the lower centers where the emotional level is found. The cortex provides means whereby emotional responses may be not only conditionally stimulated, but also conditionally inhibited. Thus emotions may be set in opposition to one another. Are we angry and tempted to take vengeance? The cortically associated consequence of punishment by society rouses fear in us, and our action is prevented. Is the soldier, terror-stricken when a shell tears his "buddie" to bits, tempted to desert? If he should, a shooting squad would confront him, the terror is suppressed and he sticks.

These cases illustrate a process which is going on continuously. No doubt in primitive tribes the checks on instinctive behavior are less numerous than in civilized communities. As men have gathered in larger and larger groups, more and more have traditions, codes and laws been imposed to prevent the free display of certain feelings and impulsive acts. Indeed,

the early years of life are characterized by what Myerson⁵ has called "the social conditioning of visceral activities" The impulses to defecate and urinate, the powerful sexual impulses, strongly stimulated in our aphrodisiac world, the impulses to avoid dangerous demands upon us and to punish those who have injured us—all these impulses are as natural as breathing, but in civilized society the cortex puts a rein upon them The emotional or impulsive thalamic level says "act," and the conditioning cortical level says "no," or "circumstances are not appropriate," or "wait awhile" A conflict arises between unconditioned and conditioned impulses And thus within a system arranged for the unification of the organism, there is antagonism between the portion stimulated to discharge and the portion inhibiting the discharge And so-called "tensions" develop, because the emotional level, stimulated to discharge but held back from external expression, can have its way *inside the body* The dog, restrained as he scents his bird, "quivers with excitement," we say The angry man, withholding his blow, likewise "quivers with excitement" But deeper than these surface showings are the viscera, which the cortex does not control There the impulsive emotional level, deprived of outward expression, still governs And the disturbed processes of digestion, the disorderly action of the heart, the fluctuating high pressures in the arteries, the accentuated state of diabetes and the interferences with menstrual function are among the consequences

The antagonism between nervous activity of the impulsive thalamic level and that of the conditioning and inhibitory cortical level may result in phenomena which the physiologist can explain only by an inferred blocking of neurone pathways Such blocking might explain the paralysis of the shell-shocked—the so-called "hysterical wound" of the terrified soldier, which resolves his conflict by taking him from danger and also by giving him a reason for his freedom Such blocking might likewise account for the exclusion of the memory of a painful or disagreeable experience On the assumption that, by blocking, neurone patterns may become dissociated during antagonistic activities in the brain, we could understand not only isolated "neurograms" of previous events, but their ability to influence, uncontrolled, the interoceptive apparatus and its visceral effectors How antagonism between the two grand divisions of the nervous system could result in the assumed dissociation of neurone patterns is quite unknown The fact of dissociated memories, however, is not questioned

CONCLUSION

In the foregoing exposition I have endeavored to show that a highly important change has occurred in the incidence of disease in our country—that serious infections, formerly extensive and disastrous, have markedly decreased or almost disappeared, and that meanwhile conditions involving strain in the nervous system have been greatly augmented The nervous

system is all-pervasive. It can have effects in remote and secluded portions of the body, far from any obvious lesion. Because it is universal in its effects, disorders which involve the nervous system require consideration of the organism as a whole. But well-nigh all diseases involve the nervous system, because they arouse fears and anxieties and worries, and these feelings are expressed in demonstrable bodily effects.

I have questioned whether we as members of the medical profession have been sufficiently aware of the altered emphasis of illness. Have we not insisted too strongly that only such pathology as can be heard or felt, or tested and measured in the laboratory, is true pathology? Have we not specialized our observations so intently that we do not see the organism because of the organs? Have we not institutionalized medical practice to such a degree that we think more of the disease than we do of the man as an individual and as a member of a social group? An affirmative answer, I believe, should be given to each of these questions.

The cults of mental healers, which have grown to extraordinary proportions, are probably a measure of the failure of the medical profession to consider adequately the rôle of emotion in producing bodily disorders. The practitioners of these cults, in so far as they are untrained laymen, ignorant of the methods of critical diagnosis, are a menace to society. Even if there were no other reason for us to recognize the part which these practitioners undoubtedly play in restoring the morale of the depressed and the anxious, there is the reason that by so recognizing their services and by taking over those services ourselves we should be safeguarding our fellow-men who are ill.

In the course of this discussion I have spoken as a physiologist. The ways in which fears and deep-seated hate and other intense emotional feelings can influence the organism have purposely been described in physiological terms. This was done in order to make clear the point that the bodily effects are as understandable and can be as reasonably explained as clenching the fist or lifting the foot. It was not done because I would neglect the subjective side of impressions and behavior. The organism may be regarded as a "mind-body" unity, and we may quite as appropriately speak of conflicts in the conscious realm as we would speak of opposed impulses in neurones—they may be regarded as different aspects of the same operating system. An attempt to speak of all psychic events in neurological terms is commonly called "neurologizing" or perhaps "physiologizing." But an attempt to designate as "psychic," processes which are demonstrably neural is quite as reprehensibly "psychologizing." If we agree that we are organized as a psycho-organismic unity we need not hesitate to use any convenient terms in mentioning any aspect of behavior or experience, for then we understand that these terms designate one aspect or the other of a living, systematic whole. On that basis we may consider the ways in which success is achieved in the treatment of emotional disorders. Problems of deep feeling may be settled by removing the occasions for them. Sup-

pressed and forgotten fears may be brought into remembrance and abolished by being interpreted. Or rage and hate may be overwhelmed by an inspiring and inclusive love, in the religious sense, which embraces even one's enemies. In all such conversions of turmoil and trouble into serenity and freedom from bodily disturbance, is not the common feature that of resolving conflicts, of bringing harmony where there was discord, of restoring a normal consistency to one's memories and one's attitude and behavior? Perhaps our examination of the physiological antagonism which can develop between the cortex and the thalamic area will reveal to some how internal warfare may profoundly affect the whole organism, and how a return of internal peace may bring miraculously a return of health and happiness. If this excursion into physiology may have that effect, my emotional level would be most pleasantly affected.

REFERENCES

- 1 CANNON, W. B. Bodily changes in pain, hunger, fear and rage, 2nd Ed., 1929, D. Appleton and Co., New York.
- 2 CANNON, W. B. The wisdom of the body, 1932, W. W. Norton and Co., New York.
- 3 FRIEDGOOD, H. B., and PINCUS, G. Studies on conditions of activity in endocrine organs, *Endocrinology*, 1935, *21*, 710-718.
- 4 BARD, P. Emotional expression after decortication, *Psychol. Rev.*, 1934, *21*, 309-449.
- 5 MYERSON, A. The social conditioning of the visceral activities, *New Eng. Jr. Med.*, 1934, *ccxi*, 189-193.

VIRUSES AND THE DISEASES CAUSED BY THEM

By THOMAS M. RIVERS, M.D., *New York, N. Y.*

INFECTIOUS diseases are caused by certain kinds of active agents or their toxins. For convenience, or for other reasons, such agents are divided into the following groups: protozoa, fungi, bacteria, spirochetes, rickettsia, and, finally, the viruses. The viruses and their relation to disease will be the subject of my talk at this time.

The diseases of man that are known to be caused by, or that are strongly suspected of being caused by viruses are measles, German measles, mumps, fever blisters, herpes zoster, varicella, smallpox, vaccinia, rabies, psittacosis, common colds, influenza, St. Louis type of encephalitis, Japanese B type encephalitis, epidemic encephalitis, lymphocytic choriomeningitis, poliomyelitis, lymphogranuloma inguinale, Australian X disease, louping ill, Rift Valley fever, yellow fever, papataci fever, dengue fever, warts, and molluscum contagiosum.

In addition to man, lower animals, insects, plants, and even bacteria are subject to virus maladies. Foot-and-mouth disease of cattle, hog cholera, canine distemper, sarcomata of chickens, fowl pox, polyhedral diseases of caterpillars, mosaic diseases of plants, and bacteriophagy are examples of virus maladies of hosts other than man. In fact, no form of life seems to be exempt from such diseases. Since much of our knowledge of viruses has come from the study of diseases of hosts other than man, physicians must take them into consideration. Consequently, I shall not apologize for references to work not dealing strictly with diseases of human beings.

Workers in the virus field are frequently confronted with the question, "What is there about viruses that induces investigators to set them apart from ordinary bacteria, protozoa, fungi, spirochetes, and rickettsia?" Such a question implies that all infectious diseases must be caused by agents falling into the well recognized groups just mentioned. Indeed, certain workers are loath to accept the idea that infectious diseases can be caused by active agents possessing a nature different from those already known. In any event, the viruses are smaller than ordinary bacteria, and the size of some, e.g., the viruses of poliomyelitis and foot-and-mouth disease, approximates that of certain protein molecules. Furthermore, the viruses have not been cultivated in vitro in the absence of living susceptible cells, and in that sense they are obligate parasites.

The nature¹ of no virus is definitely known. At present, however, three sets of ideas seem to cover the possibilities. (1) The smallest viruses, e.g., the viruses of foot-and-mouth disease and poliomyelitis, may be inanimate incitants of disease transmissible in series. Stanley² believes that the virus of tobacco mosaic is an autocatalytic substance and recently reported that he

* Presented before the General Sessions of the American College of Physicians, Detroit, March 2, 1936.

is able regularly to obtain it in crystalline form. His work is significant, and, if his interpretations of it are accepted, progress has been made in regard to the nature of certain viruses. (2) The medium-sized viruses, as exemplified by the etiological agents of yellow fever and fever blisters, may represent forms of life unfamiliar to us. (3) The virus of vaccinia^{3, 4, 5} might well be a minute living autonomous organism or a midget in the microbial world, provided the elementary bodies which are infectious and are composed of protein, fats, carbohydrates, and ash represent nothing but individual units of the virus.

That the viruses are exceedingly small and that they have not been shown capable of multiplication in the absence of living cells are not sufficient reasons for considering the variety of diseases caused by them as possessing pathological changes in common. Indeed, one is repeatedly asked "Why are smallpox, mosaic diseases, poliomyelitis, sarcomata of chickens, and bacteriophagy—diseases with such diverse clinical pictures—grouped together?"

It is now generally agreed that viruses, regardless of their nature, are intimately associated with the cells injured by them. In fact, they are believed to multiply or to be regenerated within such cells. Consequently, it is not surprising that the viruses exert a decided influence upon these parasitized cellular elements.

What effects⁶ are produced in cells by the action of viruses? If the action is not too rapid or explosive, and if the affected cells are capable of multiplication, the primary response is hyperplasia resulting in an overgrowth of tissue. In certain diseases this is the chief pathological change, and tumors, such as the sarcomata of fowls and the papillomata of rabbits, are formed. In other maladies, e.g., smallpox and varicella, the primary stimulation with its resulting hyperplasia is followed by a necrosis or destruction of the hyperplastic tissue which causes the formation of characteristic vesicles and pustules. Similar phenomena are also observed in bacteriophagy in which the lysis of the bacteria is preceded by a stimulation of the cells as evidenced by an increased rate of their growth. If the action of the viruses is explosive as in yellow fever and Rift Valley fever, no obvious hyperplasia occurs, and necrosis of cells is the first sign of disease. Finally, if the cells, e.g., nerve cells, attacked by viruses, even though the action of the viruses be slow, are incapable of multiplication, the first sign of infection is lysis or necrobiosis of the cells. Such is the case in poliomyelitis, rabies, and louping ill.

One might ask, "How important a rôle do inclusion bodies and inflammation play in the pathological pictures caused by viruses?" In the past, pathologists devoted most of their attention to these phenomena and considered them of prime importance. It is true that inclusion bodies are of great significance, but they do not occur in all virus maladies. Inflammation is seen in most virus diseases, but it is nothing more than a secondary phenomenon appearing in the wake of cellular destruction. While inclusions are

important and inflammation regularly occurs in virus maladies, hyperplasia, hyperplasia and sequent or accompanying necrosis, and necrosis are the primary pathological phenomena of virus diseases, are common to all, characterize them, and logically permit of their segregation, in spite of their diverse clinical pictures, into the same group of diseases

Inasmuch as it is obvious that certain viruses induce a marked hyperplasia of tissues, it is easy to understand why such agents are considered in discussions of the cause of cancer. In spite of the great amount of work that has been carried on in this field, the relation of virus tumors to cancer has not been determined.

I have discussed the nature of viruses and the pathological pictures produced by them. Now I shall take up the questions of prevention and treatment of virus maladies. Inasmuch as quarantine measures are of little or no value in the control of this group of diseases, I shall omit a discussion of them and pass immediately to a consideration of prevention and treatment by means of vaccines and convalescent sera, questions of lively interest at the moment, particularly in connection with poliomyelitis.

There seems to be some misunderstanding in regard to the use of the word treatment, some physicians insist that all measures instigated after exposure to an infectious agent, even though the exposed person is still well, constitute treatment, while others are in the habit of employing the word only to designate measures initiated after the onset of signs and symptoms of disease. Consequently, in order to avoid confusion, I shall, in the remainder of my talk which deals with the efficacy of vaccines and immune sera, usually indicate at what time they are administered in relation to exposure and onset of signs of disease.

The principles underlying vaccinations are old and date back to variolation and vaccination against smallpox. In variolation, the infectious agent, introduced into the body in a manner not usually encountered in nature, was supposed to produce a mild disease resulting in immunity. In vaccination, an altered virus in the form of cowpox was used to induce a mild local infection that protected against the severe malady smallpox. These principles actuated Pasteur when he prepared vaccines with an altered but active bacterium or virus. The alteration of the former agent was accidentally accomplished by prolonged cultivation of the organism on an artificial medium, while in the case of the latter agent the change was brought about by repeated passages of rabic virus in rabbits which resulted in "fixed virus." Theobald Smith went one step further and showed that injections of killed bacteria resulted in evidences of immunity in animals receiving them. In spite of the excellent work that has been done, we are still faced with the problem of the proper state of activity of viruses for vaccines and the proper methods of their administration for the prevention of virus maladies.

It is generally conceded that calf lymph is an efficacious means of preventing smallpox, but it appears that this, the oldest and best instrument of

vaccination, can be improved upon in the form of culture vaccine virus administered intradermally.⁷

Fifty years after the introduction of antirabic vaccination, there is no agreement regarding the type of vaccine that should be used. In certain places, the Pasteur type of vaccine is still administered, in others, the Hogyes vaccine consisting of freshly prepared active fixed virus is employed, according to the Harris method, repeated injections of dried active fixed virus are given, finally, the Semple vaccine is supposed to contain phenol-inactivated virus.

For the prevention of yellow fever, two vaccines have been employed, one a formalin-inactivated virus,⁸ the other an immune serum mixed with a virus altered by repeated passage through mice.⁹

Psittacosis in man is not likely to occur unless the virus enters by way of the upper respiratory tract. In view of this fact, repeated subcutaneous injections of fully active virus have been used for the vaccination of laboratory workers against the disease.¹⁰

Recently, poliomyelitic virus supposedly inactivated by formalin¹¹ and virus still active but "attenuated" by sodium ricinoleate¹² have been used for the vaccination of children against infantile paralysis.

Vaccines to be of value must be reasonably safe and in most instances should protect for more than a short period of time. Completely inactivated viruses certainly would be the safest form in which to use them as vaccines for human beings. However, there is no evidence that smallpox and yellow fever can be prevented with vaccines composed of inactive viruses. Furthermore, certain workers are inclined to doubt the value of some batches of Semple vaccine containing inactive rabic virus, because they do not produce protection in dogs against rabies. Indeed, some investigators¹³ question whether a serviceable amount of immunity can be produced by a completely inactivated rabic virus, and no one expects a prolonged state of immunity to follow vaccination even with active virus, as is evidenced by the fact that each time a person is bitten by a rabid animal a course of vaccination is given. There is no reliable evidence^{14, 15, 16} that either of the recently used vaccines for poliomyelitis is efficacious, while there is grave doubt concerning the safety of one and a certain amount of apprehension in regard to the use of the other.

Why do inactive viruses fail to serve as efficient vaccines? An exact answer to such a question is not available. It may be that some viruses, such as that of poliomyelitis, are very poor antigens even in an active state. Furthermore, the antigenic components¹⁷ of certain viruses may be so labile that they are altered or destroyed in the process of inactivation. Finally, viruses as a rule compose such a minute portion of the tissue emulsions containing them that it is not practical at present to obtain large amounts of them for administration as vaccines.

There is no reason to suppose that the general principles of immunity¹⁸ are not operative in virus diseases. Therefore, inasmuch as it is likely that

most viruses are proteins or are largely composed of proteins, one would expect them to be antigenic and to produce a certain degree of immunity even in an inactive state provided their antigenic properties were not destroyed by inactivation and sufficient amounts were given. In the past, it has not been possible to meet the provisos just mentioned in regard to most of the virus diseases of man. What will happen in the future no one knows.

Vaccines are usually given before exposure, but in the case of smallpox and rabies, vaccinations made after exposure may be efficacious. The incubation period of vaccinia is very short and the rapidly resulting immunity may prevent or modify the activity of the already implanted smallpox virus. The incubation period of rabies is sufficiently long, four weeks or more, to allow the administration of a complete course of vaccination after an individual has been bitten.

The efficacy of vaccines has frequently been estimated in terms of serological tests, and in the case of virus diseases the neutralization test is the one that has usually been employed. Unfortunately the results of neutralization tests made with serum from vaccinated animals may not parallel resistance. This is particularly true in the case of poliomyelitis^{19, 20} and rabies,¹⁸ i. e., vaccinated animals may possess neutralizing antibodies and still be susceptible, while others may be resistant in the absence of demonstrable antibodies. Indeed, such a state of affairs may follow an obvious infection with certain viruses. For instance, monkeys that have recovered from a systemic infection with equine encephalomyelitic virus possess neutralizing antibodies in their blood and are systemically resistant to reinfection, but their brains remain entirely susceptible to the action of the virus.²¹ Moreover, what takes place in one host as the result of a virus infection may not occur in another, e. g., the brains of monkeys systemically infected with equine encephalomyelitic virus do not become immune, while those of guinea pigs do become resistant under similar circumstances.²¹ Furthermore, the events occasioned by the activity of one virus in a host may not parallel those induced by another active agent in the same host as evidenced by the fact that a systemic infection of monkeys with vaccine virus²² results in an immunity of their central nervous system, while such is not the case, as just pointed out, in regard to a systemic infection with equine encephalomyelitic virus. Consequently, at present the only adequate test for the efficacy of a vaccine is its ability to prevent or modify the disease for which it is given in a specified host.

Before taking up the question of prevention and treatment of virus diseases by means of convalescent or immune sera, I shall describe two sets of experiments that throw considerable light upon the subject.

Several years ago it was shown in my laboratory that typical vaccinal lesions developed in normal rabbit corneas that had been removed from the animals, inoculated with vaccine virus, and cultivated in plasma clots *in vitro*.²³ It is an interesting fact that pathological lesions typical of this

virus malady can be produced *in vitro*, and use has been made of it to investigate certain immunological phenomena²⁴

Corneas were removed from normal rabbits and after inoculation with vaccine virus were embedded in plasma clots obtained from rabbits immune to vaccinia. Typical vaccinal lesions with Guarnieri bodies and an abundant amount of active virus developed in such tissues in spite of the fact that in the plasma surrounding them there were sufficient antibodies to fully neutralize the virus. This phenomenon is easily understood in the light of the fact that the activity of vaccine virus can not be materially influenced by immune substances or antibodies once it has made contact with or entered susceptible cells. In this respect our findings are in agreement with those of Rous and Jones²⁵ who showed that intracellularly situated typhoid bacilli and red blood cells are not susceptible to such injurious agents as potassium cyanide and antisera.

The other set of experiments to which I referred was conducted by Andrewes²⁶ who showed that antivaccinal serum infiltrated into the shaved skin of a rabbit prevented the development of a vaccinal lesion in the treated skin even though the virus was inoculated immediately afterwards. However, if the virus was injected into the skin five minutes prior to the time that the infiltrations of immune serum were made, no amount of serum sufficed to prevent a lesion, and, if eight hours were allowed to elapse after inoculation, not even the size of the lesion was influenced. Furthermore, it was demonstrated that large amounts of immune serum, administered intravenously shortly after the virus was inoculated intradermally, would prevent a generalized eruption but would exert no influence upon the lesion at the site of the inoculation. In this connection, it should be remembered that as a rule no evidence of infection is seen during the first 48 hours after vaccine virus is injected into the skin of a rabbit.

The results of the above experiments clearly indicate that once a virus has entered a cell its activity can not be influenced by large amounts of antiviral serum. Furthermore, such findings aid one in interpreting the results obtained in the use of immune sera for the prevention and treatment of virus diseases in man.

Convalescent measles serum given to a child just before and within six days after exposure to measles usually prevents the appearance of evidences of the disease, serum administered between the sixth and tenth days after exposure as a rule modifies the severity of the infection, serum given after the onset of signs of infection, which most frequently appear on the tenth day, is according to observant and critical workers without beneficial effects.

In attempts to interpret the significance of the results just described, let us assume that the virus of measles enters the upper respiratory tract and multiplies in some part not definitely determined. Beginning with the sixth day after exposure the virus is distributed from the primary focus to different parts of the body by way of the blood stream, and, from the course of events, it is not unreasonable to suppose that by the tenth day sufficient

virus has been distributed for the infection of most of the cells susceptible at that particular time in any given individual. If our assumptions are correct, serum administered during the first six days after exposure should not necessarily inhibit the multiplication of virus in the primary focus but should prevent its distribution and the development of illness and evidences of measles. Moreover, serum given between the sixth and tenth days should prevent the distribution of that part of the virus that has not already been distributed or should hinder its entry into susceptible cells not already involved, and, in view of this fact, should modify the severity of the infection but not prevent it. Finally, serum administered after the tenth day should not be beneficial, because most if not all the cells that are to be affected have by that time already been entered by the virus.

Those who are familiar with measles will say, "But the rash comes on the fourteenth instead of the tenth day." That is true. Viruses, however, may be in cells several days before evidences of the fact become obvious. Furthermore, according to some observers, a measles rash can be made evident by means of ultraviolet light 24 to 48 hours before it is detectable under ordinary conditions.

In the case of measles, many assumptions have been made regarding the location of the virus in the body at different times during the course of the infection. Unfortunately, a good experimental animal is not yet available for the testing of some of the assumptions. In the case of certain virus diseases of the central nervous system, however, there are suitable experimental animals from which accurate data have been obtained regarding the location and concentration of the viruses from the time that they are instilled into the nose until the animals die.

Fite and Webster²⁷ have shown that after instillation of louping ill virus into the nose of mice the active agent is present in the brain four days before the animals evidence signs of illness.

Galloway and Perdrau²⁸ found that after instillation of louping ill virus into the nose of monkeys the active agent was well distributed throughout the central nervous system several days before the animals showed signs of sickness.

Hurst²¹ instilled equine encephalomyelitic virus into the nose of monkeys, sacrificed them at different times after inoculation, tested various parts of their central nervous systems for the presence of the virus, and correlated his findings with clinical observations made on the monkeys before they were killed. According to him, all parts of the central nervous system except the cord contained virus within 30 hours after the onset of fever, and several hours later, at the time of the onset of nervous symptoms, even the lumbar cord was infectious.

Webster and Clow²⁹ dropped the virus of the St. Louis type of encephalitis into the nose of mice, sacrificed some at different times in order to test for the presence of virus in various parts of the brain and cord, killed others to determine the time of appearance and progression of lesions, and

allowed others to sicken and die in order to determine the time of onset of clinical signs and symptoms. The data obtained in this manner clearly showed that virus was present in the tissues 24 to 48 hours before the appearance of lesions detectable under the microscope, and that all parts of the brain and cord contained large amounts of virus before the animals became ill.

Fabel and Gebhardt³⁰ conducted similar experiments with monkeys that had been infected by means of intranasal instillation of poliomyelitic virus. Their findings indicate that by the fifth, sixth, or seventh day after inoculation, at which time only an occasional rise of temperature or tremor and hyperesthesia were present and before paralysis had occurred, virus was distributed throughout the central nervous system.

In view of the above mentioned results obtained by a number of workers by means of many experiments with different viruses in different hosts, it seems logical to assume that the virus of poliomyelitis by the time signs and symptoms of disease become obvious in infected human beings has already reached practically all of the nerve cells that are likely to be attacked. If such be the case, then one would expect convalescent serum given after the onset of signs of the disease to be valueless. Indeed, such expectations are in accord with the clinical findings reported by careful workers who have used the serum for therapeutic purposes under properly controlled conditions both in monkeys and in human beings.

If the factors described above as being responsible for the therapeutic failures of convalescent poliomyelitic serum are not operative in every case, there are others that enhance the likelihood that failures will regularly occur, such as the inability of antibodies to penetrate the blood-brain barrier and reach the virus in the tissues of the brain and cord. Furthermore, it is highly improbable that antibodies in potent antisera placed in the subarachnoid space are capable of reaching virus situated in the depths of the brain and cord, because drainage from the subarachnoid space is as a rule not back into the central nervous system but into the general circulation.

In the first part of the talk, I discussed problems relating to the nature of viruses and the character of lesions produced by them, while in the latter section I dealt with matters pertaining to the prevention and treatment of virus diseases by means of vaccines and convalescent or immune sera. I have presented data of a general rather than a concrete nature in the hope of initiating a train of thought that will lead to a greater appreciation of problems in the virus field and a better understanding of phenomena daily encountered in the practice of medicine.

REFERENCES

- 1 RIVERS, T. M. Nature of viruses, *Physiol. Rev.*, 1932, **11**, 423-452.
- 2 STANLEY, W. M. Isolation of crystalline protein possessing properties of tobacco-mosaic virus, *Science*, 1935, **81**, 644-645.
- 3 CRAIGIE, J. Nature of vaccine flocculation reaction, *Brit. J. Exper. Path.*, 1932, **3**, 259-268.

- 4 PARKER, R F, and RIVERS, T M Immunological and chemical investigations of vaccine virus Part I, Jr Exper Med, 1935, lxi, 65-72
- 5 HUGHES, T P, PARKER, R F, and RIVERS, T M Immunological and chemical investigations of vaccine virus Part II, Jr Exper Med, 1935, lxi, 349-352
- 6 RIVERS, T M General aspects of pathological conditions caused by filterable viruses, Am Jr Path, 1928, iv, 91-124
- 7 RIVERS, T M, and WARD, S M Jennerian prophylaxis by means of intradermal injections of culture vaccine virus, Jr Exper Med, 1935, lxi, 549-560
- 8 HINDLE, E Yellow fever vaccine, Brit Med Jr, 1928, i, 976-977
- 9 FINDLAY, G M Immunization against yellow fever, Lancet, 1934, ii, 983
- 9 SAWYER, W A, KITCHEN, S F, and LLOYD, W Vaccination against yellow fever with immune serum and virus fixed for mice, Jr Exper Med, 1932, lv, 945-969
- 10 RIVERS, T M, and SCHWENTKER, F F Vaccination of monkeys and laboratory workers against psittacosis, Jr Exper Med, 1934, lx, 211-238
- 11 BRODIE, M, and PARK, W H Active immunization against poliomyelitis, Am Jr Pub Health, 1936, xxvi, 119-125
- 12 KOLMER, J A Vaccination against acute anterior poliomyelitis, Am Jr Pub Health, 1936, xxvi, 126-135
- 13 SHORTT, H E, MCGUIRE, J P, BROOKS, A G, and STEPHENS, E D Anti-rabic immunization, Indian Jr Med Res, 1935, xxi, 537-556
- 14 GILLIAM, A G, and ONSTOTT, R H Results of field studies with poliomyelitis vaccine, Am Jr Pub Health, 1936, xxvi, 113
- 15 RIVERS, T M Immunity in virus diseases—particularly poliomyelitis, Am Jr Pub Health, 1936, xxvi, 136-142
- 16 LEAKE, J P Discussion of poliomyelitis, Am Jr Pub Health, 1936, xxvi, 148
- 17 CRAIGIE, J, and WISHART, F O Agglutinogens of a strain of vaccinia elementary bodies, Brit Jr Exper Path, 1934, v, 390-398
- 18 RIVERS, T M Pathologic and immunologic problems in the virus field, Am Jr Med Sci, 1935, cxc, 435-445
- 19 SCHULTZ, E W, and GEBHARDT, L P On problem of immunization against poliomyelitis, Calif and West Med, 1935, xliii, 111-112
- 20 OLITSKY, P K, and COX, H R Active immunization against experimental poliomyelitis virus, Jr Exper Med, 1936, lxiii, 109-125
- 21 HURST, E W Infection of the Rhesus monkey (*macaca mulatta*) and the guinea pig with the virus of equine encephalomyelitis, Jr Path and Bact, 1936, xlii, 271-302
- 22 RIVERS, T M, SPRUNT, D H, and BERRY, G P Attempts to produce acute disseminated encephalomyelitis in monkeys, Jr Exper Med, 1933, lviii, 39-51
- 23 RIVERS, T M, HAAGEN, E, and MUCKENFUSS, R S Development in tissue cultures of intracellular changes characteristic of vaccinal and herpetic infections, Jr Exper Med, 1929, i, 665-672
- 24 RIVERS, T M, HAAGEN, E, and MUCKENFUSS, R S A study of vaccinal immunity in tissue cultures, Jr Exper Med, 1929, i, 673-685
- 25 ROUS, P, and JONES, F S Protection of pathogenic microorganisms by living tissue cells, Jr Exper Med, 1916, xxiii, 601-612
- 26 ANDREWES, C H Antivaccinal serum, Jr Path and Bact, 1929, xxxii, 265-272
- 27 FITE, G L, and WEBSTER, L T Distribution of virus of louping-ill in blood and brains of intranasally infected mice, Proc Soc Exper Biol and Med, 1934, xxxi, 695-696
- 28 GALLOWAY, I A, and PERDRAU, J R Louping-ill in monkeys, infection by nose, Jr Hyg, 1935, xxxv, 339-346
- 29 WEBSTER, L T, and CLOW, A D The limited neurotropic character of the encephalitis virus (St Louis type) in susceptible mice, Jr Exper Med, 1936, lxiii, 433-448
- 30 FABER, H K, and GEBHARDT, L P Localization of the virus of poliomyelitis in the central nervous system during the preparalytic period, after intranasal instillation, Jr Exper Med, 1933, lvii, 933-954

THROMBOPENIC PURPURA, AN ANALYSIS OF 160 CASES ¹

By W M FOWLER, M D , *Iowa City, Iowa*

THE present concept of thrombopenic purpura as a definite syndrome has gradually been evolved and separated from the maze of hemorrhagic diseases. In the earliest fragmentary descriptions of purpura it was noted in association with the pestilent fevers,¹ later it was found apart from these, and still more recently was separated as a distinct entity. A proper understanding of the condition, however, awaited the discovery of the blood platelets by Donne and Arnold ² and the observation by Denys ³ and Hayem ⁵ that the platelets were diminished in certain cases of purpura. This feature was subsequently verified by numerous observers and forms the basis for the syndrome which is characterized by (1) a diminished number of platelets, (2) prolonged bleeding time but an essentially normal coagulation time, (3) a non-retractile clot, and (4) a positive constrictor or arm band test. A simple classification which is similar to that of Pratt ⁷ and Rosenthal ⁸ is as follows

- I Idiopathic Thrombopenic Purpura
 - (1) Acute
 - (2) Chronic
- II Secondary Thrombopenic Purpura
 - (1) Infections
 - (2) Toxins and drugs
 - (3) Blood dyscrasias
 - (4) Diseases of the liver
 - (5) Miscellaneous

There are many reports of hereditary hemorrhagic diseases in the literature, and among these are some cases which present the clinical and laboratory features of thrombopenic purpura ^{9, 10, 11}. Although these do not constitute a large group, they occur with sufficient frequency, so that an hereditary type of thrombopenic purpura must be acknowledged.

Since many conditions may lead to the clinical manifestations of purpura without the characteristic hematological features, and especially without a reduction of the platelets, the universal recognition of thrombopenic purpura as a distinct syndrome has been delayed, and there has been much confusion in the literature. The early classifications of purpura were based purely on the clinical features, and this has been continued in spite of more recent and improved methods of blood examination. The criteria given above for the diagnosis of thrombopenic purpura eliminate from this discussion the simple purpuras so common in youth and senility, the anaphylactoid purpura with

* Received for publication January 25, 1936
From the Department of Internal Medicine, State University of Iowa

abdominal and joint manifestations (Henoch-Schonlein), the purpuras due to avitaminosis (scurvy) as well as those cases of purpura associated with vascular changes which occur with many acute infections and intoxications

IDIOPATHIC THROMBOPENIC PURPURA

The pathogenesis of idiopathic thrombopenic purpura has given rise to much discussion¹² and cannot be considered as definitely settled. That the platelets originate from the megakaryocytes in the bone marrow,¹³ have a life of but a few days,¹⁴ and are destroyed by the spleen, is quite generally accepted. They accelerate coagulation,² improve the degree of syneresis,¹⁵ and perhaps play some part in combating infections and in the production of anaphylactic reactions. Their rôle in thrombopenic purpura is not clear, and some deny the existence of this syndrome as separate from those forms of purpura in which the clinical manifestations are similar, but in which the platelets are present in normal numbers.¹⁶ If we accept the syndrome as possible of recognition we must consider the cause of the platelet deficiency to determine whether it results from under-production of platelets, as originally proposed by Frank,¹⁷ or from their over-destruction by the spleen.¹⁸ We may further consider the possibilities of the actual loss of platelets through hemorrhage, the formation of defective platelets which are removed by the spleen, or the removal of platelets from the circulation in an attempt to control the capillary hemorrhage. For a further discussion of the cause and the effects of this reduction in the number of platelets the reader is referred to the work of Mackay,² Lescher and Hubble,¹⁹ and De Sanctis and Allen.²⁰ The most generally accepted theory is that a deficiency in platelets is the primary feature of the condition and that bone marrow insufficiency is responsible for this deficiency. The possibility has been advanced, however, that there are two types of thrombopenic purpura, as yet indistinguishable by clinical means, one of which is due to deficient or faulty production of platelets while the second results from their increased destruction by the spleen.

The close association of thrombopenic purpura, aplastic anemia and agranulocytosis and the similarity of many of their features have been emphasized. The three diseases have been grouped together under the term "marrow insufficiency"^{21,22}. Their occurrence under similar conditions, their frequent association and the origin of each of the cell types within the bone marrow give credence to this correlation and, in certain cases, cause difficulty in the differential diagnosis. Although presenting distinct and separate clinical features in most instances, there are certain borderline cases with an overlapping of the hematological pictures, as might be expected when the histogenesis of the various cell types is considered.

The histologic changes in the bone marrow and spleen are varied and have tended to confuse rather than clarify our concept of the pathogenesis. Studies of the bone marrow have not been numerous in cases of idiopathic thrombopenic purpura, and in those in which they have been made, the find-

ings are divergent. Those cases in which the megakaryocytes are diminished in number or possess shrunken and pyknotic nuclei lend support to Frank's theory¹⁷. In other cases with an equally low platelet count, the megakaryocytes of the bone marrow are present in normal numbers and show no morphologic changes^{23, 24}. This group tends to support Kaznelson's theory¹⁸ that the bone marrow is not the seat of the primary disorder. Lawrence and Knutti²⁴ studied the bone marrow of six patients, four of these showed no abnormalities and two had a diminished number of megakaryocytes. They suggest, as did Lescher and Hubble,¹⁹ that in those patients with normal bone marrow the primary lesion is in the spleen with a resultant increased destruction of normally formed platelets, and that these are the patients who show improvement after splenectomy. It is interesting to note that experimental production of thrombopenic purpura by means of antiplatelet serum has led to equally divergent histological findings in the bone marrow²⁵.

Certain cases show hyperplasia of the marrow,²⁶ either diffuse or patchy, as a regenerative response to repeated hemorrhages. All the elements of the marrow may take part in the hyperplasia, even the megakaryocytes.

Examination of the spleen reveals no uniformity in the histologic picture, so that the findings are not specific or diagnostic. In many instances the spleen is essentially normal, and in others, as in two of those removed in this clinic there is a simple fibrosis. In many instances the spleen is enlarged and presents endothelial cell hyperplasia of both the sinuses and Malpighian corpuscles²⁷. The lymphoid elements may be diminished, normal, or increased, and the platelets within the spleen may be increased or entirely absent.² Thickening of the arterial walls in the vessels to the follicles has been noted in some instances.

With such a diverse histologic picture in both spleen and bone marrow, one can but conclude that there is no uniform pathological change and at present can but speculate as to the possibility of two distinct types of idiopathic thrombopenic purpura.

SECONDARY THROMBOPENIC PURPURA

An enormous number of case reports have appeared in the literature showing the association of thrombopenic purpura with a wide variety of primary disorders and intoxications. One can find no feature present in all cases to explain the diminution in platelets so that the pathogenesis is just as obscure as in the idiopathic form. In certain instances definite bone marrow pathology is present to account for the thrombopenia while in others a chemical or bacterial toxin which either destroys the platelets or inhibits their production has been hypothesized. The bone marrow may be fatty or aplastic in cases of marrow insufficiency, it may be hyperplastic with an overgrowth of myeloid or lymphatic elements in leukemia, or may show no essential histologic change in cases of infection or intoxication.

The hyperplasia of aleukemic myelosis may be found in a biopsy of the sternum or a lymph node²⁸ so that this procedure is worthy of consideration in obscure cases

CLINICAL FEATURES

The clinical features are the same in both the idiopathic and secondary types. The diagnosis of thrombopenic purpura must rest on the laboratory findings of prolonged bleeding time, positive constrictor test, non-retractile clot and lowered blood platelets rather than on the clinical picture. Hemorrhage into the skin, either as purpuric spots or as ecchymoses, is the most characteristic feature, the former frequently appearing spontaneously with successive crops of innumerable small hemorrhages on the extremities, neck and upper trunk, while the latter may occur as a result of a very minor trauma. These skin manifestations are not uniformly present and their absence may forestall the correct diagnosis. Many patients have hemorrhages from the mucous membranes of the nose, mouth, gastrointestinal or genito-urinary tracts without involvement of the skin. Painless uterine hemorrhage is a frequent manifestation of this syndrome in women, and hemoptysis, hematuria, and cerebral hemorrhage are not uncommon. These hemorrhagic manifestations are so frequently present without skin involvement that thrombopenic purpura must be considered in all cases of unexplained hemorrhage. In many of the cases which are secondary to other disease there are no hemorrhagic manifestations, and the diagnosis is made purely on the laboratory data found on routine hematological examination. In other instances the hemorrhagic features overshadow the primary condition. In the idiopathic variety, which is more common in females and usually appears early in life, there is frequently a history of having bled or bruised easily since birth.

The blood picture in the idiopathic cases is that of a post-hemorrhagic anemia, and although certain morphological changes in the platelets have been described,²⁹ they are not constant enough for diagnostic purposes. The reduction in the number of platelets varies, but Minot²² has given 60,000 per cu mm as the critical level below which hemorrhage is apt to occur. We have used the thrombocyto-crit method of Van Allen³⁰ for platelet determinations, since in our hands it has been more reliable for routine use than platelet counts.

Complete hematological studies have been done in 160 cases of thrombopenic purpura. Of these, 17 were found to be of the idiopathic type, and 143 were secondary thrombopenic purpura. The further subdivision of these groups is best shown in the following tabulation. The subgroups will then be discussed separately.

ANALYSIS OF CASES

- | | | |
|---|---------------------------------|----|
| I | Idiopathic Thrombopenic Purpura | |
| | (1) Acute | 3 |
| | (2) Chronic | 14 |

II Secondary Thrombopenic Purpura		143
(1) Infection	25	
(2) Toxins and drugs	6	
(3) Blood dyscrasias	81	
Lymphatic leukemia		18
Lymphoma		11
Myelogenous leukemia		15
Aleukemic myelosis		7
Acute (stem cell) leukemia		1
Pernicious anemia		14
Aplastic anemia		11
Familial hemolytic icterus		1
Acquired hemolytic icterus		1
Anemia of pregnancy		1
Idiopathic hypochromic anemia		1
(4) Liver disease	12	
(5) Miscellaneous	19	

SECONDARY THROMBOPENIC PURPURA

BLOOD DYSCRASIAS

Leukemia Under the heading secondary thrombopenic purpura the largest group, 81 cases, was associated with disease of the hematopoietic system, and of these leukemia was the most frequent. There were 18 cases associated with lymphatic leukemia, in four of which it appeared as a terminal event in the chronic, slowly progressing form in adults. The other 14 cases occurred in association with the more acute rapidly progressing lymphatic leukemia of childhood, nine of which were in the subleukemic state described by Abt³¹ and Hyland³². There were 15 cases of myelogenous leukemia complicated by thrombopenic purpura. In the early stage of myelogenous leukemia the platelets are not infrequently increased in number, so that the complication occurred as a terminal event in the chronic cases but appeared early in the course of the acute forms. Thrombopenic purpura was present in each of the seven cases of aleukemic myelosis which we have studied, and the resultant hemorrhagic tendencies were the predominant feature of the illness. One case of acute blast cell leukemia was accompanied by this syndrome. It is apparent that thrombopenic purpura is most apt to appear in the acute rapidly progressing forms of leukemia, but may occur as a terminal event in the more chronic forms. It very definitely adds to the gravity of the prognosis inasmuch as it signifies a more rapid course. In some instances the hemorrhagic features are the most striking part of the clinical picture, giving rise to difficulties in diagnosis, especially in the aleukemic forms in which the blood picture is not diagnostic. Examination of the bone marrow either by biopsy or sternal puncture may be necessary for a correct interpretation.

Lymphoma Thrombopenic purpura was a less frequent complication in the other forms of lymphoma than was true of lymphatic leukemia. Eleven cases were found, four of which occurred with the sclerosing type (Hodgkin's disease) and seven with the lymphoblastic and lymphocytic type without leukemia. Although not a common causative agent, these diseases

must be considered as possibilities when thrombopenic purpura appears, even though splenomegaly and lymphadenopathy are not prominent. The presence of this complication adds to the gravity of the prognosis, since it appears more commonly in the rapidly progressing forms or as a terminal feature in the chronic cases.

Pernicious Anemia In 14 patients thrombopenic purpura was found associated with pernicious anemia, a much lower incidence than with leukemia. In none of these patients were the hemorrhagic features of purpura clinically apparent except for a tendency to bruise more easily than normal or to bleed more readily from slight trauma, and the syndrome was discovered only by routine blood examinations. A reduction in the platelet count is a characteristic feature of pernicious anemia, and it is surprising that thrombopenic purpura does not occur more frequently with this disease. This complication did not influence the course nor the prognosis of pernicious anemia, and with an induced remission the platelets returned to a normal level. One case of thrombopenic purpura was found in each of the following conditions, in none of which did it produce any clinical manifestations: acquired hemolytic icterus, familial hemolytic icterus, idiopathic hypochromic anemia and anemia of pregnancy.

Aplastic Anemia There were 11 cases of idiopathic aplastic anemia, seven adults and four children, in which thrombopenic purpura was present. The clinical manifestations of purpura were present in all but one of these cases, and frequently were the predominant feature. The diagnosis of aplastic anemia was verified by necropsy in three of the patients who died in the hospital. There were certain borderline cases in which it was difficult to differentiate between idiopathic thrombopenic purpura and aplastic anemia, but in all of the above cases the anemia seemed to be the primary feature, appearing before the hemorrhagic features rather than being dependent on the loss of blood. The association of the two conditions is almost constant in the late stages of aplastic anemia, and the severe hemorrhages hasten the end in most instances.

LIVER DISEASE

Various forms of liver disease are well recognized as a cause of thrombopenic purpura, and 12 such instances were encountered in this series. The mechanism by which the platelets are affected is not known although with the seat of fibrinogen formation in the liver, it is not surprising to find changes in blood coagulation and syneresis. The clinical features of purpura were prominent in only one of these patients, and spontaneous hemorrhages did not appear in the others in spite of the presence of laboratory features of the syndrome. The appearance of the complication, regardless of the severity of its manifestations, adversely affected the prognosis. In this group there were seven cases of Banti's syndrome, one of which was syphilitic in origin, four cases of portal cirrhosis and one of syphilis of the liver.

TOXINS AND DRUGS

A review of the literature reveals that thrombopenic purpura is frequently the result of the administration of various drugs, and cases have been reported after arsphenamine,³³ bismarssen,³⁴ gold,³⁵ quinine,³⁶ bismuth,³⁷ and iodine.³⁸ In the present series only six similar instances were found. Three appeared with the administration of arsenic, two followed the application of organic hair dye, and one was associated with chronic benzol poisoning. In all of this group the associated anemia was severe and of the aplastic type.

MISCELLANEOUS

Among the miscellaneous diseases there were many entirely unrelated conditions giving rise to this complication. Included in the group were four cases of carcinoma, two of the breast and one each of the stomach and pancreas. Three of these had given rise to widespread metastasis with bone involvement, while the one arising in the pancreas had no demonstrable metastatic lesions. There was one case of extramedullary myeloblastoma without evident bone involvement and one case of melanosarcoma. One patient with myxedema presented this syndrome, as did one with Graves' disease who had not received iodine. There was one case of chronic glomerulo-nephritis. A roentgen-ray technician developed the typical laboratory features of this syndrome together with a mild degree of anemia, although there were no hemorrhagic manifestations. With greater precautions against exposure to roentgen-rays the blood returned to normal. A patient with xeroderma pigmentosum developed the typical features of aplastic anemia, agranulocytosis and thrombopenic purpura, with severe hemorrhages from the nose, mouth and gastrointestinal tract. At autopsy, however, no aplasia of the sternal or rib marrow was apparent.

There were eight cases on whom no additional information was available so that the primary lesion, if any, is unknown. No cases were found in which an allergic reaction was responsible for the thrombopenia, although such cases are numerous in the literature and it has been demonstrated that the administration of an allergen to a susceptible individual produces a distinct drop in the platelet count.³⁹

INFECTION

The importance of infection as an etiological agent in secondary thrombopenic purpura has been repeatedly emphasized, and the eradication of foci is recognized as an essential feature in the treatment of the idiopathic cases. In many instances it is difficult to evaluate with certainty the rôle which infection plays in the etiology. In the present series there were 25 patients in whom it was felt that infection was undoubtedly the cause. Only six of these occurred in adults, two of whom had subacute bacterial endocarditis and one had broncho-pneumonia. One male, aged 27, had repeated attacks of gonorrheal urethritis with a subsequent arthritis and prostatitis. Epi-

sodes of purpura and hemorrhage appeared with the acute exacerbations of urethritis, and in addition to the characteristic findings of thrombopenic purpura there was a moderate anemia and agranulocytosis. At necropsy there was no evidence of aplasia of the bone marrow. In one patient, a female aged 34, severe nasal, gingival and uterine hemorrhages, together with an extensive purpuric eruption, followed immediately an acute upper respiratory infection. On admission to the hospital the specific laboratory features of thrombopenic purpura were present, and the gums were so swollen and bloody as to suggest leukemic infiltration. Biopsy of both gums and bone marrow presented a normal histologic picture. One year later the blood was normal in every respect and there had been no recurrence of the hemorrhagic features. Another girl, aged 17, had repeated episodes of purpuric eruption for four years and more recently had two severe episodes of hemorrhage. The first appearance of purpura was immediately after diphtheria so that it was difficult to determine whether the infection was the primary etiological factor or whether the infection merely precipitated the onset in a patient with potential or latent idiopathic thrombopenic purpura.

Infection as an etiological agent plays a more important rôle in children than in adults, and 19 cases secondary to infection were found in patients under 14 years of age. In one child military tuberculosis not only caused the typical laboratory and clinical features of thrombopenic purpura but also a differential blood picture almost indistinguishable from lymphatic leukemia. Necropsy examination revealed a generalized military tuberculosis with involvement of the bone marrow. Tuberculosis appears in the literature as a frequent causative agent and has even been suggested as the responsible agent in most cases of the idiopathic form.⁴⁰ One typical example of thrombopenic purpura with severe hemorrhages occurred during the course of epidemic parotitis and one during an acute infectious enteritis. Three cases were associated with septicemia, a condition which is prone to produce not only this syndrome but also an aplastic anemia, and it is difficult at times to determine whether the septicemia was the primary factor or occurred as a terminal event. There were five cases which appeared in association with measles, either during the period of eruption or during convalescence. Acute upper respiratory infections were most common in producing this syndrome in children, and there were eight cases in which the ears, tonsils or sinuses were involved. It is more commonly associated with an acute infection but occurs also with chronic forms. Acute exacerbations of the infection may cause recurrent attacks of hemorrhage as in one six year old boy who had repeated hemorrhagic episodes over a period of a year, each accompanying an acute exacerbation of otitis media. In none of the cases secondary to infection which we have been able to follow has there been a recurrence of symptoms after eradication of the infection. This propensity of infection to cause thrombopenic purpura supports the

contention that all obvious foci should be removed even in those patients with an apparently idiopathic form

IDIOPATHIC THROMBOPENIC PURPURA

The diagnosis of idiopathic thrombopenic purpura must rest not only on the presence of the characteristic laboratory and clinical manifestations, but also on the rigid exclusion of all diseases which may cause the secondary form. Certain cases, especially in elderly patients with no preceding evidences of hemorrhage, are undoubtedly considered as idiopathic only because of our inability to locate the primary trouble. Remissions can be induced by blood transfusion in the majority of idiopathic cases and should be done as a diagnostic as well as therapeutic measure before more radical procedures are undertaken. In the acute fulminating type, which is frequently fatal in spite of blood transfusions, splenectomy is usually of no avail so that the delay for diagnostic purposes is justifiable.

Seventeen cases in this series were considered to be idiopathic in origin, nine occurring in adults and eight in children under 14 years of age. Among the adult cases, one, a female aged 24, was acutely fatal, the first episode of hemorrhage being uncontrollable by any means at our disposal. One male, aged 38, had bruised easily for many years but had no hemorrhages or purpuric spots until two years before admission to the hospital. The bleeding at this time was easily controlled by transfusion, and further therapeutic procedures were postponed so as to determine the subsequent course. There have been no recurrences as yet. One male, aged 50, had recurrent hemorrhages for 38 years, and two other elderly patients gave histories of intermittent hemorrhages and purpura of many years' duration. The same history of recurrent hemorrhages and purpura was obtained in the younger adults, so that in all cases the actual onset of symptoms was in childhood or early adult life. Splenectomy was not performed in any of this group.

The ages of the children with idiopathic thrombopenic purpura ranged from four to 14 years and were equally divided between males and females. Two of these eight cases were of the acute type. One of these died of cerebral hemorrhage soon after admission. The bleeding was controlled in the other acute case, she returned home and in the subsequent 12 months has had no recurrence except a mild epistaxis during the course of measles. The remaining six cases were of the chronic type and gave histories of hemorrhage or of bruising easily for from one to several years, and in one instance, in a boy of six, these features had been noted by the parents since birth. One chronic case, on which a splenectomy was advised, but was refused by the parents, died after returning home. Transfusions were given to all patients in this group to control the hemorrhage, and the response was good in all instances except one case that died of hemorrhage. Foci of infection were eradicated when present at

tomy was performed on three patients. Two of these three patients were subsequently followed and there has been complete disappearance of symptoms. The histologic picture in one spleen was normal while the other two showed only simple fibrosis. Two of the patients who did not have a splenectomy have had no recurrence of symptoms in the year which has elapsed since they were discharged from the hospital.

TREATMENT

The treatment of secondary thrombopenic purpura depends entirely upon the primary condition, and in those cases in which this can be eliminated the purpuric manifestations disappear. The prognosis in those cases associated with infections, pernicious anemia and other conditions responding to therapy, is good whereas little can be accomplished in the others. For immediate control of the hemorrhage transfusion of whole blood is indicated, either intramuscularly, or preferably intravenously. This is effective in many instances although in those with acute leukemia, aleukemic myelosis and aplastic anemia, it usually has but little effect. Various coagulants and hemostatics have been tried but are of little avail, and we have found no case in which these were entirely successful. Since splenectomy is acutely fatal in many of these cases and of no avail in the others, the necessity of an accurate diagnosis cannot be stressed too strongly.

There is no universal agreement as to the proper treatment of the idiopathic form of thrombopenic purpura. Since infections play so prominent a rôle in the production of the secondary forms as well as precipitating attacks in the idiopathic variety, they should be eradicated when present regardless of whether they are definitely related to the symptoms or not. Special diets,⁴¹ high vitamin intake and calcium salts have been advocated but a specific effect has not been definitely proved. Antivenin⁴² has been used with some success and snake venom has been recommended for its temporary hemostatic effect^{43, 44}. Peptone shock therapy has been advocated⁴⁵ and we have experienced some success in certain hemorrhagic diseases by sensitizing the patient to horse serum and then producing an anaphylactic reaction. The use of roentgen-rays over the spleen has been found to be of only temporary value⁴⁶ and ligation of the splenic artery has been proposed but not generally accepted.

Splenectomy should be considered in the idiopathic form only when the diagnosis has been established with absolute certainty. Many of these cases tend to improve spontaneously with advancing age, and the symptoms may completely or almost completely disappear in adult life so that removal of the spleen is unnecessary. In other cases the hemorrhage is not sufficient to warrant splenectomy, even at the onset of the illness. Since remissions induced in practically all cases of idiopathic thrombopenic purpura of transfusion, it is best to watch the patient through one or more determine the severity and frequency of the hemorrhages. If

they are severe and show no evidence of diminishing intensity, the spleen should be removed during a quiescent period. The operation carries a high mortality in the acute stages so that it is justifiable to attempt to carry the patient through this stage by transfusions. Splenectomy may produce a complete cure, an amelioration of symptoms, or the condition may recur with equal severity. At the present time there is no definite criterion on which to base the prognosis following splenectomy, although it is hoped that sternal biopsy or puncture may eventually give this information. The operation is best withheld until it has been determined whether the attacks are becoming more severe, until the effects of transfusion have been noted and until the effectiveness of eradication of focal infections has been determined. Spence,²⁷ in recording the results of splenectomy in 101 cases, found good results in 90.9 per cent of the chronic and 16.6 per cent of the acute cases. Whipple⁴⁷ collected 81 cases and found 6 deaths among 73 chronic cases and 7 deaths in 8 acute cases. Sixty-one patients were followed postoperatively and 51 had good results, 4 were fairly successful and 6 were not relieved. It has been repeatedly emphasized that protection against infections is an extremely important feature in the postoperative care of the patient.

SUMMARY

One hundred and sixty cases of thrombopenic purpura have been studied with respect to the etiology, prognosis and treatment. It was found that 143 of these cases were of the secondary type.

The importance of infection in the etiology of secondary thrombopenic purpura and its significance as a precipitating factor in the idiopathic cases have been emphasized.

The diagnostic difficulties have been mentioned, and the importance of an accurate diagnosis and of a proper period of observation prior to splenectomy in all cases is stressed.

BIBLIOGRAPHY

- 1 JONES, H. W., and TOCANTINS, T. M. The history of purpura hemorrhagica, *Ann Med Hist*, 1933, v, 349-359.
- 2 MACKAY, W. The blood platelet: its clinical significance, *Quart Jr Med*, 1931, xxiv, 285-328.
- 3 DENYS, J. Quoted by Duke.⁴
- 4 DUKE, W. W. The pathogenesis of purpura hemorrhagica with especial reference to the part played by blood-platelets, *Arch Int Med*, 1912, x, 445-469.
- 5 HAYEM, G. Du Purpura, *Presse med*, 1895, 233.
- 6 DUKE, W. W. The relation of blood platelets to hemorrhagic disease, *Jr Am Med Assoc*, 1910, lv, 1185-1192.
- 7 PRATT, J. H. (in OSLER and McCRAE. *Modern medicine*, 1908, iv, 681-716.)
- 8 ROSENTHAL, N. The blood picture in purpura, *Jr Lab and Clin Med*, 1928, xiii, 303-322.
- 9 WITTS, L. J. The hereditary hemorrhagic diathesis, *Guv's Hosp Rep*, 1932, lxxvii, 465-474.

- 10 ROSENFELD, A S Idiopathic purpura with unusual features, *Arch Int Med*, 1921, *xxviii*, 465-474
- 11 KROMEKE, F Zur Frage der hereditären haemorrhagischen Diathese (Thrombasthenie), *Deutsch med Wchnschr*, 1922, *xlvi*, 1102-1105
- 12 PAYNE, R L, and WHITEHEAD, R C Purpura hemorrhagica (thrombocytopenia) An evaluation of our present knowledge, *Internat Clin*, 1934, *ii*, 188-205
- 13 WRIGHT, J H The histogenesis of the blood platelets, *Jr Morphol*, 1910, *xxi*, 263-278
- 14 DUKE, W W The rate of regeneration of blood platelets, *Jr Exper Med*, 1911, *xiv*, 265-273
- 15 TOCANTINS, L M Platelets and the spontaneous syneresis of blood clots, *Am Jr Physiol*, 1935, *cx*, 278-286
- 16 TIDY, H L Hemorrhagic diathesis, *Lancet*, 1926, *ii*, 365-369
- 17 FRANK, E Die essentielle Thrombopenie, *Berlin klin Wchnschr*, 1915, *liii*, 490-494
- 18 KAZNELSON, P Verschwinden der hamorrhagischen Diathese bei einem Falle von essentieller Thrombopenie (Frank) nach Milzexstirpation Splenogene thrombolytische Purpura, *Wien klin Wchnschr*, 1916, *xxix*, 1451-1454
- 19 LESCHER, F G, and HUBBLE, D A correlation of certain blood-diseases on the hypothesis of bone-marrow deficiency or hypoplasia, *Quart Jr Med*, 1932, *i*, 425-455
- 20 DE SANCTIS, A G, and ALLEN, A W Purpura hemorrhagica, *Am Jr Dis Child*, 1931, *xli*, 552-567
- 21 MIDDLETON, W S, and MEYER, O L Marrow insufficiency, *ANN INT MED*, 1935, *viii*, 1575-1590
- 22 MINOT, G R Diminished blood platelets and marrow insufficiency, *Arch Int Med*, 1917, *xix*, 1062-1084
- 23 MINOT, G R Studies on a case of idiopathic purpura hemorrhagica, *Am Jr Med Sci*, 1916, *clii*, 48-65
- 24 LAWRENCE, J S, and KNUTTI, R E The bone marrow in idiopathic thrombopenic purpura, *Am Jr Med Sci*, 1934, *clxxxviii*, 37-41
- 25 LEE, R I, and ROBERTSON, O H The effect of antiplatelet serum on blood platelets and experimental production of purpura hemorrhagica, *Jr Med Res*, 1916, *xxxiii*, 323-336
- 26 FALCONER, E H, and MORRIS, L M A clinical comparison of aplastic anemia, idiopathic purpura hemorrhagica and aleukemic leukemia based on studies of the bone marrow, *Med Clin N Am*, 1922, *vi*, 353-370
- 27 SPENCE, A W The results of splenectomy for purpura hemorrhagica, *Brit Jr Surg*, 1928, *xv*, 466-499
- 28 BALDRIDGE, C W, and FOWLER, W M Aleukemic myelosis, *Arch Int Med*, 1933, *lii*, 852-876
- 29 BLACHER, L Recherches experimentale sur les methodes d'exploration et sur la morphologie des thrombocytes ainsi que sur leur importance clinique en tant que systeme autonome, *Le Sang*, 1935, *ix*, 147-183
- 30 VAN ALLEN, C M Volume measurement of blood platelets, *Jr Lab and Clin Med*, 1926, *xii*, 282-285
- 31 ABT, I A A case of aleukemic leukemia with clinical symptoms of aplastic anemia, *Med Clin N Am*, 1924, *viii*, 427-436
- 32 HYLAND, C M Lymphatic leukemia without leukocytosis, *Am Jr Dis Child*, 1930, *xxxix*, 59-65
- 33 MCCARTHY, F P, and WILSON, R The blood dyscrasias following arsphenamines, *Jr Am Med Assoc*, 1932, *xcix*, 1557-1563
- 34 NILES, H D Hemorrhagic purpura following bismarsen, *Am Jr Syph Neurol*, 1934, *xxviii*, 300-305
- 35 JONES, H W, TOCANTINS, L M, and CORSON, E F Purpura hemorrhagica, intravenous gold as an etiological factor, *Penn-Med Jr*, 1934, *xxxvii*, 809-811
- 36 DE CECILCO, C Purpura hemorrhagica-syndrome due to quinine, *Gior veneto di sc med*, 1934, *viii*, 815-821

- 37 BIANCHI, A E Consideraciones sobre un caso de purpura, Rev Assoc med Argent, 1932, xlv, 1566-1574
- 38 DENNIG, H Thrombopenische Purpura nach Jodennahme, Munchen med Wchnschr, 1933, lxxx, 562
- 39 SQUIER, T L, and MADISON, F W Thrombocytopenia due to food allergy (Presented at the Central Society for Clinical Research in Chicago, Nov 2, 1935)
- 40 GARIN, G Hemorrhagic purpura and tuberculosis, Riforma Med, Naples, 1920, xxxvi, 952 (Abstr, Jr Am Med Assoc, 1921, lxxvi, 276)
- 41 KUGELMASS, N Clinical control of chronic hemorrhagic states in childhood, Jr Am Med Assoc, 1930, cii, 204-210
- 42 TAYLOR, K P A Antivenin in thrombocytopenic hemorrhage, Am Jr Surg, 1933, xxi, 285-288
- 43 GREENWALD, H M Dilute snake venom for the control of bleeding in thrombocytopenic purpura, Am Jr Dis Child, 1935, lxx, 347-352
- 44 PECK, S M, and ROSENTHAL, N Effect of moccasin snake venom (Ancistrodon Piscivorus) in hemorrhagic conditions, Jr Am Med Assoc, 1935, civ, 1066-1070
- 45 PARSSEAU and ALCHECK Peptone shock treatment in hemorrhagic purpura, Bull et mem Soc med d hop d Par, 1923, xlvii, 258 (Abstr, Jr Am Med Assoc, 1923, lxxx, 1736)
- 46 PANCOAST, H K, PENDERGRASS, E P, and FITZ-HUGH, T The present status of the roentgen-ray treatment of purpura hemorrhagica by irradiation of the spleen, Am Jr Roent, 1925, xiii, 558-567
- 47 WHIPPLE, A O Splenectomy as a therapeutic measure in thrombocytopenic purpura hemorrhagica, Surg, Gynec and Obst, 1926, xlii, 329-341

THE THERAPEUTIC EFFECT OF SOLUTION OF POTASSIUM ARSENITE IN CHRONIC MYELOGENOUS LEUKEMIA *

By D J STEPHENS, M D , and JOHN S LAWRENCE, M D ,
Rochester, New York

For many years roentgen therapy has been the most satisfactory method of treatment of the chronic leukemias. It is generally agreed that life is not materially prolonged by irradiation, but in favorable cases symptomatic and hematologic improvement occurs for variable periods of time. Some patients experience uncomfortable reactions to treatment, others become refractory to irradiation, and occasionally an alarming depression of the red and white blood cells occurs. In the absence of specific forms of therapy for the disease, there is need of other palliative measures which may be used in place of, or in conjunction with, roentgen therapy. Interest in the use of solution of potassium arsenite was revived in 1931 by the reports of Forkner and Scott^{1 2}. These authors observed striking symptomatic and hematologic improvement in nine of ten cases of chronic myelogenous leukemia, treated for short periods of time with toxic or subtoxic doses of solution of potassium arsenite (Fowler's solution). During the past three years several reports discussing the treatment of leukemia have contained brief mention of arsenic as one of the useful drugs in the treatment of chronic myelogenous leukemia, but detailed confirmation of these observations has not appeared in the available literature.

Material for this report consists of seven patients with chronic myelogenous leukemia treated with one or more prolonged courses of solution of potassium arsenite, and observed for periods of from several months to three years. In five patients, arsenic therapy has been supplemented by roentgen treatments. In general our conclusions confirm and amplify those of Forkner and Scott.

Except for short periods of observation in the hospital, patients were followed either in the office or the Out-Patient Department, where frequent clinical and hematologic observations were made. Differential blood counts were made in films prepared on cover slips, stained with Wright-Giemsa stain. Schilling's classification of the leukocytes was used. In the figure both the myelocyte and the juvenile of this classification are included "myelocytes". Solution of potassium arsenite was given in rapidly increasing doses until toxic symptoms appeared, subsequent dosage was regulated as necessary to maintain a subtoxic level of the drug. Iron, when given, was prescribed in the form of 12 Bland's pills or six grams of ferrous

* Received for publication January 31, 1936

From the Department of Medicine, School of Medicine and Dentistry, University of Rochester, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, New York

ammonium citrate daily. Roentgen-ray treatments, as indicated in roentgen units, were given over the spleen or chest. The course of each patient will be discussed briefly in relation to an accompanying chart, in which changes in the hemoglobin, the red and white blood cell counts and the differential counts are shown. Non-essential details are omitted from the case reports.

CASE REPORTS

Case 1 D S, a 58 year old salesman, was admitted to the Strong Memorial Hospital on February 2, 1934. During the previous six months he had noted fatigue, shortness of breath on exertion and loss of 15 lbs in weight. For about one month before admission to the hospital there had been intermittent abdominal pain, weakness, anorexia and pallor. Two weeks previously his physician had found a white blood cell count of 167,000, had made a diagnosis of leukemia and prescribed Fowler's solution in doses of 10 drops three times daily. The development of conjunctivitis of the right eye prompted his admission to the hospital.

In 1931 a diagnosis of coronary occlusion had been made. This was followed by thrombophlebitis in the right leg, which incapacitated him for a period of about six months. A white blood cell count of 16,000 was noted during this illness.

On examination the patient appeared chronically ill, was pale and apparently had lost weight recently. He had an acute catarrhal conjunctivitis on the right. There were several small retinal hemorrhages. The edge of the spleen was palpable 8 centimeters below the costal margin. The liver edge was felt 8 centimeters below the costal margin and was tender. There was a moderate degree of benign prostatic hypertrophy.

Laboratory findings. Blood hemoglobin 6.4 gm per 100 c.c., red blood cells 1,990,000 per cu mm, white blood cells 193,000 per cu mm. The differential leukocyte formula was as follows: eosinophiles, 1 per cent, myeloblasts, 1.5 per cent, myelocytes, 37 per cent, juveniles, 2 per cent, stab neutrophils, 2.5 per cent, segment neutrophils, 52.5 per cent, lymphocytes, 1.5 per cent. Platelets were abundant. Blood non-protein nitrogen was 61 mg per cent, uric acid, 4.76 mg per cent, serum albumin, 4.72 gm per cent, serum globulin, 2.2 gm per cent, creatinine, 2.6 mg per cent. Basal metabolic rate was plus 31 per cent. The urine showed a small amount of albumin, an occasional granular cast and red blood cell. The electrocardiograph showed left axis deviation, without other abnormalities.

The conjunctivitis subsided within a few days. During February three doses of deep roentgen-ray therapy were given over the spleen and chest. A moderate drop in the total leukocyte count occurred but there was no change in the percentage of immature cells and no clinical improvement. Shortly after admission to the hospital the patient developed difficulty in urination, presumably due to prostatic obstruction. On February 21, the blood non-protein nitrogen was 92 mg per cent, creatinine, 6.2 mg per cent, uric acid, 8.7 mg per cent. Detailed studies of kidney function were not done because of the precarious condition of the patient.

On March 7, two weeks after the last roentgen-ray treatment, weakness, fatigue and dyspnea had increased, the total leukocyte count had risen to the previous level and the anemia had become more severe. No change had occurred in the size of the spleen or liver. The urinary symptoms had disappeared but the non-protein nitrogen was 75 mg per cent, creatinine, 5.3 mg per cent, uric acid, 7.8 mg per cent. At this time the administration of Fowler's solution was begun.

On April 13, arsenic was discontinued because of nausea and vomiting, which subsided within a few days. At this time the leukocyte count was 15,200 per cubic millimeter, of which only 9 per cent were immature cells. The strength and appetite had improved, and he had gained weight during the period of arsenic therapy. There

had been some decrease in the size of the spleen. There had been no urinary symptoms, and urinalysis showed no abnormalities. On April 23, the blood non-protein nitrogen was 48 mg per cent, uric acid, 40 mg per cent. An increase in the reticulocytes, which reached 12 per cent, was followed by striking improvement in the anemia. The administration of iron in the form of 12 Bland's pills per day was begun on April 26, and he received a blood transfusion on May 2. It should be noted that the reticulocyte response and the increase in hemoglobin and red blood cells occurred before the institution of the latter procedures.

In May, because of return of the leukocyte count and percentage of immature cells to a high level, the administration of Fowler's solution was resumed. Clinical improvement continued, he gained further weight, and there was no significant change in the level of blood non-protein nitrogen or uric acid. There was again a gradual decrease in the total white blood cell count to a value but little above normal. The decrease in percentage of immature cells was less striking. In July, Fowler's solution was again discontinued because of weakness, anorexia and diarrhea. These symptoms disappeared within a few days. There had been little change in the size of the spleen. Without therapy the leukocyte count rose again and remained high. In spite of a moderate degree of anemia, he felt quite well, without undue fatigue or weakness, during the next four months. Treatment was omitted during this period because of the satisfactory clinical condition.

In December he was again admitted to the hospital with fever and respiratory difficulty of a few days' duration. There were signs of pneumonia of the lower lobe of the left lung. The spleen was somewhat larger than it had been previously. At this time the blood non-protein nitrogen was 110 mg per cent, uric acid, 107 mg per cent, creatinine, 50 mg per cent. The patient died, apparently as the result of pneumonia, a few hours after admission to the hospital.

The autopsy findings were characteristic of chronic myeloid leukemia. All bone marrow sections showed marked myeloid hyperplasia. There were extensive myeloid infiltrations in the spleen, which weighed 2175 grams, in the liver, which weighed 3800 grams, and in the kidneys. Bronchopneumonia was present in both lungs. Canalization of an old thrombus in the right femoral vein had occurred. There was nothing to indicate that the typical pathologic picture of chronic myelogenous leukemia had been altered by the previous arsenic therapy.

Case 2 M. V., a 24 year old housewife, was first seen in the Out-Patient Department October 23, 1933 complaining of abdominal pain of an indefinite nature. During the previous year she had lost about 15 pounds in weight. For about two months she had noted "weakness of the eyes" and had been unable to read or sew. There had been some fatigue on exertion but no limitation of activity.

Examination showed moderate pallor, no glandular enlargement. Ophthalmoscopic examination revealed bilateral papilledema. The retinal veins were engorged and tortuous, of irregular caliber, in some areas they were barely visible. There were several old retinal hemorrhages. The spleen was enlarged, extending to the right of the umbilicus with its lower border palpable 22 cm below the costal margin.

Blood hemoglobin was 89 gm per 100 cc, red blood cells, 2,750,000 per cu mm, white blood cells, 322,000 per cu mm. Differential formula was as follows: basophiles, 15 per cent, eosinophiles, 2 per cent, myelocytes, 46.5 per cent, juveniles, 8 per cent, stab neutrophils, 18.5 per cent, segment neutrophils, 22 per cent, lymphocytes, 15 per cent. One nucleated red blood cell per 100 leukocytes was found. Platelets were abundant.

Within two weeks after starting Fowler's solution the eyes had improved, strength had returned and the abdominal discomfort had diminished. There was gradual decrease in the total leukocyte count and percentage of immature cells. The anemia improved. The spleen gradually became smaller and in May 1934 could not

be felt The eyegrounds became normal in appearance and remained so From February 1934 until the time of her death, almost a year later, the patient was without symptoms except those attributed to mild arsenic intoxication, which occurred from time to time For a period of 10 months before death the leukocyte count was within, or slightly above normal limits and the immature cells remained below 5 per cent During the period of arsenic therapy, which was continued in subtoxic doses without interruption for 15 months, a diffuse, tan colored pigmentation with some dryness of the skin appeared and persisted over the entire body

During the latter part of January, the patient died at home, of pneumonia, after an acute illness of three days' duration Autopsy was not done

Case 3 J L, a 54 year old retired miller, was admitted to the Strong Memorial Hospital December 29, 1932 complaining of weakness and fever He had suffered from fatigue and general malaise for about six months For the past six weeks he had been weak, tired and "feverish" He had had drenching night sweats, anorexia, dyspnea on slight exertion and had lost 25 pounds in weight

On examination, the temperature was 39° C He appeared chronically ill and had evidently lost weight There were small soft lymph glands in each axilla There were small hemorrhages in each ocular fundus and one small petechial hemorrhage in the left buccal mucosa The spleen extended six centimeters below the costal margin

Blood hemoglobin was 10.5 gm per 100 c.c., red blood cell count was 3,700,000 per cu mm, white blood cell count was 91,600 per cu mm The differential leukocyte formula was as follows basophiles, 2 per cent, eosinophiles, 4 per cent, myelocytes, 30 per cent, juveniles, 12.5 per cent, stab neutrophils, 11.5 per cent, segment neutrophils, 35 per cent, lymphocytes, 4 per cent Platelets were present in normal numbers

Two doses of deep roentgen-ray therapy, totalling 350 roentgen units given over the spleen, resulted in a marked reduction in the total leukocyte count and in the percentage of immature cells There was gradual clinical improvement, with increase in strength and disappearance of fever Additional roentgen-ray therapy was given in January and February In February 1933, the administration of Fowler's solution was begun and was followed by further improvement In March the spleen was barely palpable The patient returned to work and remained symptom free for several months

In September 1933 while still taking Fowler's solution, fatigue, weakness, chills and fever, and splenomegaly returned A single roentgen treatment was followed by disappearance of the above symptoms for several months In October, toxic symptoms necessitated reduction of the dose of Fowler's solution, which was finally discontinued in January 1934 During the next four months the patient received four roentgen-ray treatments because of weakness, fatigue, fever and increase in the leukocyte count and immature cells Each treatment was followed by temporary improvement in symptoms and in the white blood cell picture The anemia became progressively more severe A temporary rise in red blood cells and hemoglobin followed a transfusion early in May 1934 The patient died at home early in June 1934 Autopsy was not done

Case 4 E G, a 51 year old housewife, was admitted to the Strong Memorial Hospital on January 22, 1935 For about 18 months she had noted increasing fatigue, slight pallor and some dyspnea on exertion Five weeks before admission to the hospital there had been an acute illness characterized by fever, malaise, sore throat and non-productive cough During this illness her physician found a white blood cell count of 80,000 and made a diagnosis of leukemia A single dose of roentgen-ray therapy had been given, followed by reduction in the white blood cell count to 41,000 Fowler's solution was prescribed in doses of 15 drops daily During the last few days before admission to the hospital an itching eruption had appeared in both inguinal regions

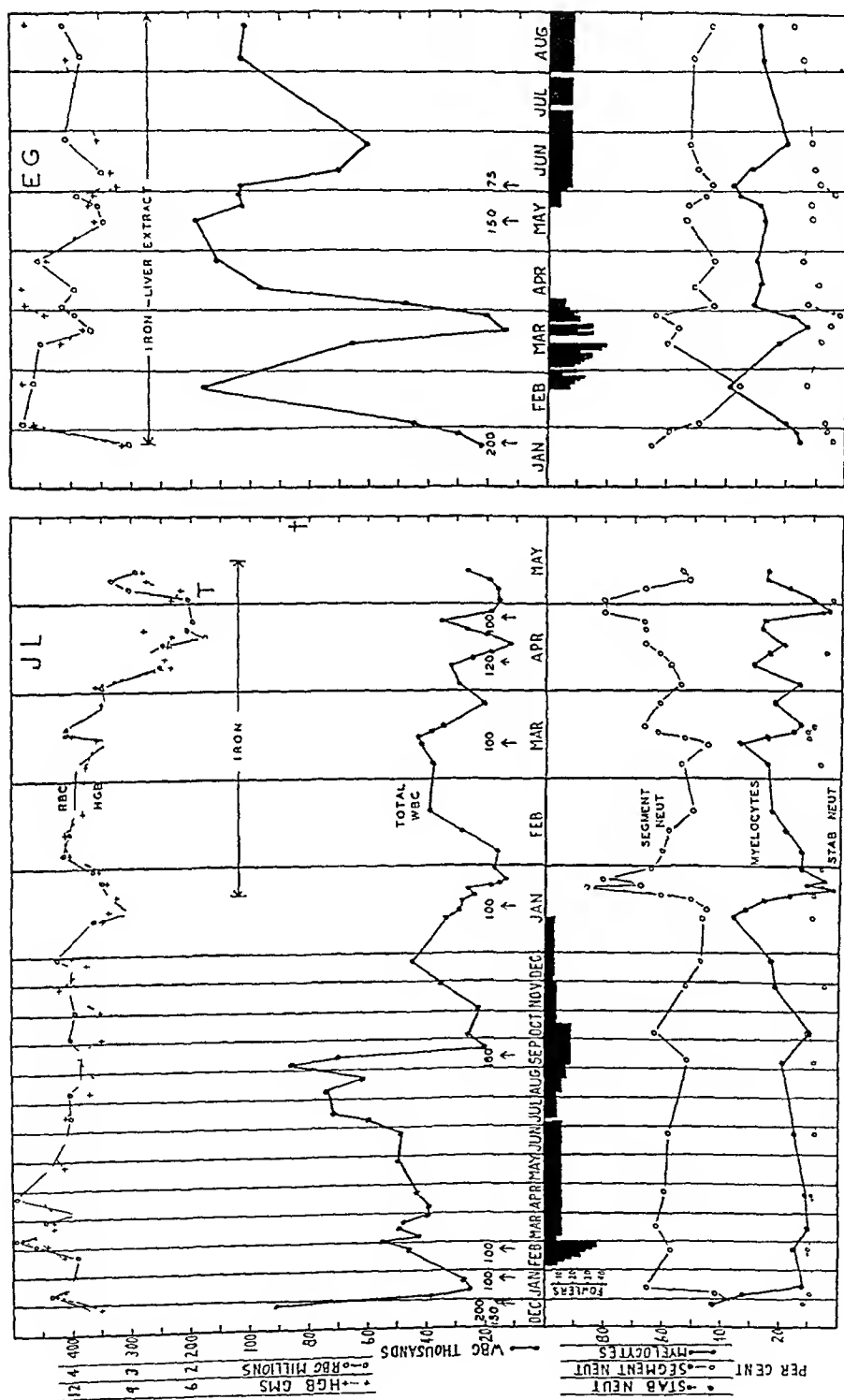


Fig. 2 Case 3 (J L), and Case 4 (E G) The daily dose of solution of potassium arsenite is indicated in drops per day. Roentgen treatments are indicated by arrows, with the dose in roentgen units. T indicates transfusion.

Physical examination showed a maculo-papular, erythematous eruption in the right axilla, in the pubic and inguinal regions, and over the labia majora. The edge of the spleen was palpable under the costal margin.

Blood hemoglobin was 9.75 gm per 100 cc, red blood cells 3,090,000 per cu mm, white blood cells 22,900 per cu mm. The differential leukocyte count was as follows: basophiles, 3 per cent, eosinophiles, 8 per cent, myelocytes, 7.5 per cent, juveniles, 7.5 per cent, stab neutrophiles, 6 per cent, segment neutrophiles 59.5 per cent, lymphocytes, 4.5 per cent. Platelets were plentiful.

A single dose of roentgen-ray therapy was given over the perineal and suprapubic regions. It was thought at the time that the skin lesions might be a form of leukemia cutis. Subsequent observations, however, indicated that the eruption was an arsenic dermatitis and that the blood picture had been favorably influenced by the previous arsenic therapy. Iron and Lilly's liver extract No. 55 were prescribed. During the following month, the skin lesions completely cleared but weakness and fatigue continued and the total leukocyte count and percentage of immature cells increased. The administration of Fowler's solution resulted in a striking diminution in the number of leukocytes and percentage of immature cells, fatigue and weakness were markedly improved. However, symptoms of arsenic toxicity appeared, and were accompanied by an itching skin eruption similar in character and location to that previously observed. This became so bothersome that Fowler's solution had to be discontinued, two weeks later the skin lesions had disappeared.

Without arsenic, the leukocyte count rose rapidly, the percentage of immature cells increased, the anemia again became more severe, and fatigue and weakness returned. A single dose of roentgen-ray therapy in May resulted in a severe reaction with prostration, increased weakness, anorexia, nausea and vomiting for several days. A smaller dose of roentgen-ray therapy two weeks later resulted in a similar but less marked reaction. The administration of Fowler's solution was again started on May 20 and continued in subtoxic amounts. Although the changes in the white blood cell picture were not striking, symptomatic relief was experienced, and improvement in the anemia was noted. At the time of writing, the clinical condition is satisfactory and the spleen is not palpable, although the total white blood cell count and the percentage of immature cells are quite high.

Case 5 N. E., a 20 year old unmarried waitress, was admitted to the Rochester Municipal Hospital September 30, 1932, with a history of chronic fatigue and loss of 20 pounds in weight during the previous year. For two days before admission there had been sharp, cramplike pains in the abdomen, without other symptoms.

Examination showed a chronically ill young woman, who appeared pale and tired. There were several ecchymoses over the legs. The spleen was markedly enlarged, extending to the right beyond the mid-line and downward to the iliac crest. A leathery friction rub was heard over the splenic area.

At the time of admission blood hemoglobin was 7.5 gm per 100 cc, red blood cells, 2,720,000 per cu mm, white blood cells 439,000 per cu mm. Differential count was as follows: basophiles, 3.5 per cent, eosinophiles, 1 per cent, myeloblasts, 1 per cent, myelocytes, 38 per cent, juveniles, 14 per cent, stab neutrophiles, 15 per cent, segment neutrophiles, 24.5 per cent, lymphocytes, 2 per cent, degenerated cells, 1 per cent. Two nucleated red blood cells were seen in counting 100 white blood cells. Platelets were abundant. Basal metabolic rate was plus 30 per cent.

The administration of Fowler's solution in increasing amounts was begun on October 2 and continued for six weeks in subtoxic doses, with occasional rest periods because of toxic symptoms. During the latter part of October there was a sharp decrease in the total white blood cell count, accompanied by a decrease in immature cells and followed by an increase in the red blood cell count and hemoglobin. These changes were accompanied by marked symptomatic improvement, disappearance of the abdominal discomfort and splenic friction rub, and diminution in size of the spleen.

On November 18, 1932 the patient was discharged to her physician in a neighboring state. She received one roentgen-ray treatment during the second week in December. When last seen on January 20, 1933 she was symptomatically well and there had been further improvement in the anemia. The total leukocyte count, however, had risen to 160,000. The further course of this patient is not known.

Case 6 M T, a 50 year old housewife, was admitted to the Strong Memorial Hospital on March 21, 1934 complaining of a mass in the abdomen. During the preceding year she had noted increasing fatigue and backache, palpitation and dyspnea on exertion and left-sided abdominal enlargement. During the past six months there had been loss of 35 pounds in weight and a chronic non-productive cough. For two months before admission there had been occasional skin hemorrhages without antecedent trauma.

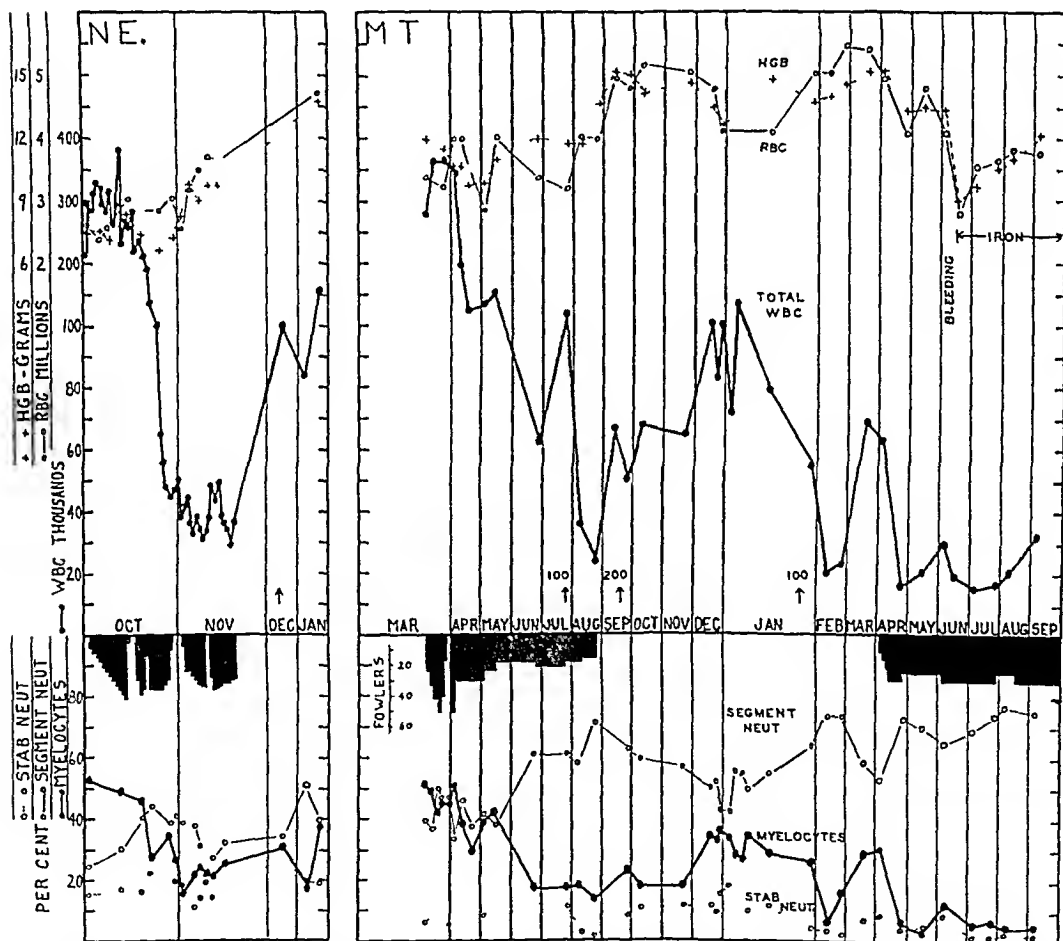


FIG 3 Case 5 (N E), and Case 6 (M T). The daily dose of solution of potassium arsenite is indicated in drops per day. Roentgen treatments are indicated by arrows, with the dose in roentgen units.

The patient was an obese woman, appearing chronically ill. The spleen extended to the right beyond the midline and downward to the iliac crest.

Blood hemoglobin was 12 gm per 100 cc, red blood cells numbered 3,800,000 per cu mm, white blood cells, 275,000 per cu mm. Differential leukocyte formula was as follows: eosinophiles, 3 per cent, myelocytes, 40 per cent, juveniles, 11 per

cent, stab neutrophils, 6 per cent, segmented neutrophils, 39 per cent, lymphocytes, 1 per cent Platelets were abundant Basal metabolic rate was plus 57 per cent

Fowler's solution was administered in subtoxic doses during the next five and a half months During this time there was a moderate decrease in the total leukocyte count and in the percentage of immature neutrophils The patient gained in weight and strength, the respiratory symptoms disappeared, the spleen decreased in size and the eyegrounds cleared In July, 100 roentgen units of roentgen-ray therapy were administered to the lateral splenic and thoracic areas, this was followed by an increase in the red blood cells and hemoglobin and by further reduction in the white blood cell count During the latter part of August, Fowler's solution was discontinued because of generalized itching and an exfoliative eruption in the pubic region Within three weeks the skin lesions had cleared A single roentgen-ray treatment in September apparently did not influence the blood picture In January 1935 the third roentgen-ray treatment was given because of fatigue and weakness This was followed by symptomatic improvement and by a sharp but temporary reduction in the total leukocyte count and the percentage of immature cells

In April 1935, the administration of Fowler's solution resulted in a precipitous decrease in the total leukocyte count and in the percentage of immature cells Since that time strength and endurance have remained good and the white blood cell count and the percentage of myelocytes in the peripheral blood have been relatively low However, the spleen, which could not be felt in April, gradually increased in size When last seen, in September, the edge of the spleen was palpable 10 cm below the costal margin, in spite of the favorable blood picture

In June 1935, tooth extraction was followed by profuse hemorrhage for a period of about 10 days Blood smears taken before and during the bleeding showed an abundance of platelets The bleeding was finally controlled by a pressure splint, but resulted in a marked increase in the degree of anemia This patient also has had occasional episodes of vaginal bleeding, controlled by gynecological measures The bleeding time and coagulation time have been normal There has been no apparent correlation of the pelvic bleeding with fluctuations in the blood picture

Case 7 J N, a 36 year old farmer, was admitted to the Strong Memorial Hospital September 9, 1932 complaining of pain in the abdomen There had been increasing weakness for the past 20 months For several weeks he had noted anorexia, fatigue, dyspnea on exertion and loss of 20 pounds in weight During the three days previous to admission there had been sharp pain in the upper left abdominal quadrant aggravated by cough, deep breathing, and changes in position

Examination showed an appearance of chronic illness, pallor, small lymph nodes in the cervical and inguinal regions There were numerous fresh and old retinal hemorrhages The spleen was enlarged, with the lower border extending downward to the level of the umbilicus A friction rub was audible over the splenic area

Blood hemoglobin was 8.6 gm per 100 cc, red blood cells numbered 2,660,000 per cu mm, white blood cells 176,000 per cu mm The differential leukocyte formula was as follows eosinophils, 1.5 per cent, myeloblasts, 2 per cent, myelocytes, 43 per cent, juveniles, 21 per cent, stab neutrophils, 8 per cent, segment neutrophils, 21 per cent, lymphocytes, 2.5 per cent Platelets were present in approximately normal numbers Basal metabolic rate was plus 29 per cent

The administration of subtoxic doses of Fowler's solution resulted in a striking diminution in the number of leukocytes and in the percentage of immature cells, but both increased rapidly when the administration of arsenic was discontinued (figure 4) The administration of Fowler's solution in amounts as large as could be tolerated again resulted in striking hematologic improvement which persisted for about three weeks after discontinuing the drug The leukocyte count was reduced to a normal value and immature cells almost entirely disappeared from the peripheral circulation Meanwhile there had been steady clinical improvement Symptoms present on ad-

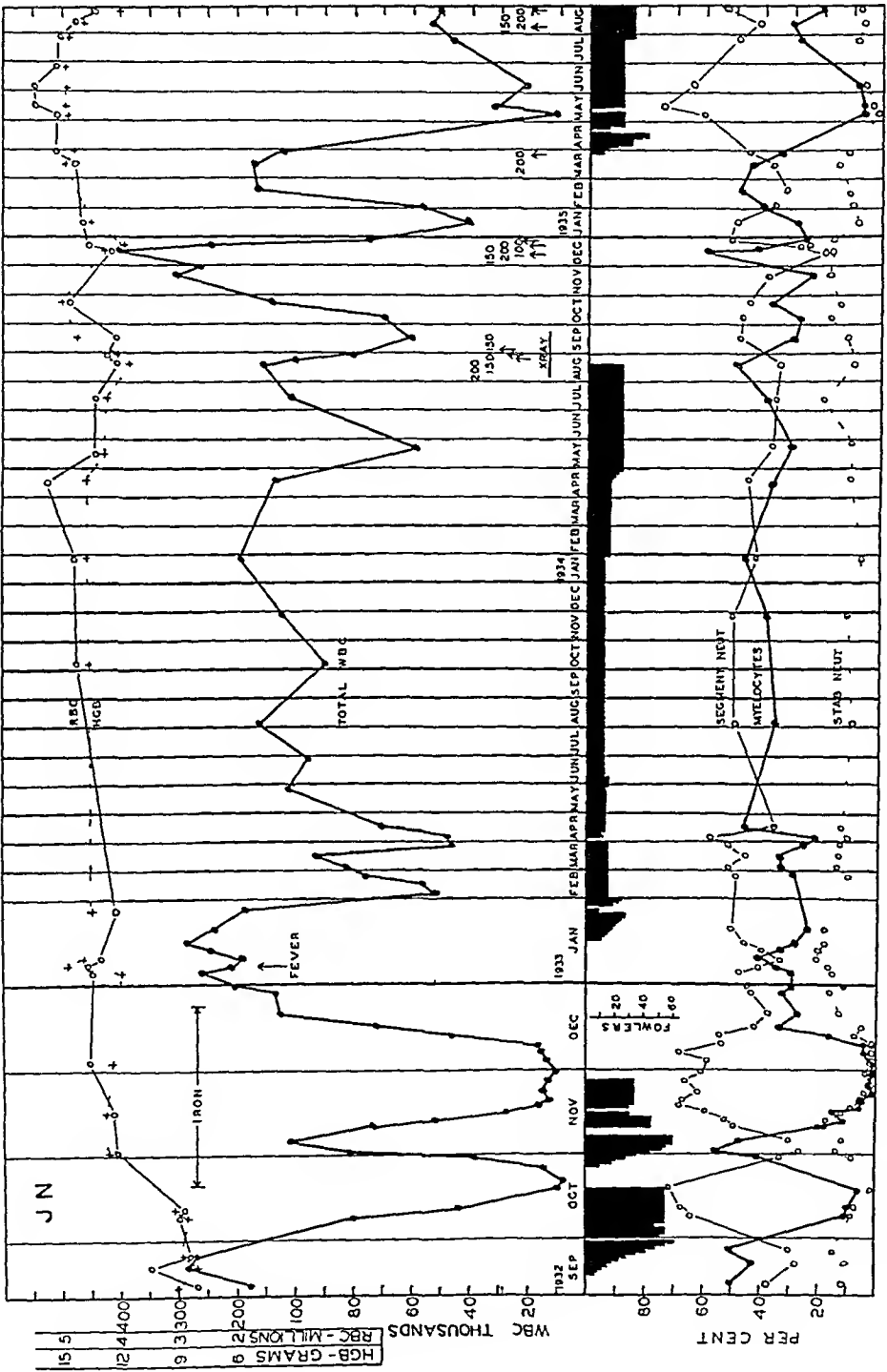


FIG 4 Case 7 (J N) The daily dose of solution of potassium arsenite is indicated in drops per day Roentgen treatments are indicated by arrows, with the dose in roentgen units

mission disappeared. The patient gained 20 pounds in weight and returned to work. In December 1932, the spleen was palpable under the costal margin.

Without therapy the total leukocyte count and the percentage of immature cells rapidly increased. On January 6, 1933, the patient submitted to 4 hours of artificial fever at a temperature of 40.5 to 41.0° C as an experimental procedure. Except for a temporary increase in hemoglobin, there was no significant change in the hematologic or clinical picture.

On January 15, 1933, the administration of Fowler's solution was again begun and was continued in subtoxic doses without interruption for 19 months. During this period the total leukocyte count and the percentage of immature cells remained relatively high. However, a satisfactory red blood cell and hemoglobin level was maintained, the splenic edge remained at the costal margin, the patient worked regularly as a laborer and was symptom-free except for intermittent, mild manifestations of arsenic toxicity.

During the month of August 1934, there was rapid increase in the size of the spleen to the level of the umbilicus and return of fatigue and weakness, shortness of breath and abdominal fullness. Arsenic was temporarily discontinued. During the next six months two courses of roentgen-ray therapy were given over the spleen. Each of these resulted in temporary clinical improvement, slight reduction in the size of the spleen, and a moderate decrease in the total leukocyte count and the number of immature cells.

In April 1935, the administration of Fowler's solution was again resumed and resulted in striking hematologic and clinical improvement. He again became symptom-free and was able to return to work regularly as a laborer in a gravel pit. The spleen was reduced in size so that the edge was palpable at the costal margin. Solution of potassium arsenite was continued, but within a few months the leukocyte count and the percentage of immature cells again began to rise and nucleated red blood cells appeared in the peripheral blood. The spleen gradually increased in size and the patient developed fatigue, non-productive cough and night sweats. In August, roentgen therapy was again begun.

DISCUSSION

It is apparent from the above case reports and charts that solution of potassium arsenite is an effective palliative agent in the treatment of chronic myelogenous leukemia. Symptomatic improvement was reported by the majority of patients soon after the administration of the drug was begun. In several instances, symptoms referable to the leukemia completely (but temporarily) disappeared. As a rule symptomatic improvement was accompanied by gain in weight, reduction in the size of the spleen and by improvement in the blood picture.

The hematologic changes in each patient are presented in detail in the charts. Soon after the toxic dose of arsenic was reached, in the characteristic response, the total leukocyte count began to fall sharply and in many instances approached the normal value. Decrease in the total white blood cell count was accompanied by a diminution in the percentage of immature cells, so that the white blood cell picture as a whole approached normal. The most striking response was observed in M V, for a period of several months the only abnormality present in the leukocyte counts was the presence of less than 5 per cent of myelocytes. The degree of hematologic improve-

ment varied from patient to patient, and in the same patient with successive courses of the drug. For example, J N experienced two striking hematologic and symptomatic remissions. The third course of Fowler's solution resulted in no significant change in the total or the differential leukocyte counts, but he remained symptom free for a period of 18 months, during which administration of the drug was continued. After a rest period during which roentgen therapy was used, arsenic again resulted in a striking, but temporary, hematologic and clinical remission. A similar variability in response was observed in M T and in E G with successive courses of the drug.

Anemia, which was present to some degree in all cases, was favorably affected. As a rule, increase in the red blood cell count and hemoglobin did not occur until a significant reduction in the total white blood cell count had taken place. In one patient (D S) a reticulocyte response was observed, followed by a sharp increase in the red blood cells and hemoglobin. It should be noted in the chart that the maximum reticulocyte response occurred before the administration of iron. It is possible that improvement in the anemia was dependent on the changes in the white blood cell picture, rather than constituting a direct effect of the arsenic. When nucleated red blood cells were present in the smears before the administration of Fowler's solution, they disappeared from the peripheral blood as the white blood cell picture and the anemia improved. Although there was originally no significant decrease in platelets in any of the patients studied, a favorable response to the arsenic therapy was usually accompanied by an increase in the platelets, easily detected in the smears.

Omission of the drug resulted, in a few weeks, in return of symptoms, increase in the size of the spleen and increase in both the total leukocyte count and the percentage of immature cells.

In attempting to maintain the dose of solution of potassium arsenite as near as possible to the minimum toxic level, each patient experienced repeated toxic symptoms. These included diarrhea, anorexia, nausea and vomiting, itching and puffiness of the eyelids, lacrimation and generalized itching of the skin. Three patients developed localized skin eruptions, characterized by small areas of erythema, dryness, scaling and itching. Three patients complained of tingling in the fingers and toes. In one individual, the soles of the feet became diffusely reddened, tender and slightly swollen. In one instance, herpes zoster of the ophthalmic division of the fifth nerve appeared while Fowler's solution was being administered. It is of interest that herpes zoster appeared in one of Forkner's patients under similar circumstances. Symptoms of arsenic toxicity disappeared within a few days after reduction in dose or omission of the drug. No alarming or serious reactions were encountered. Evidence of hepatic, renal or serious skin lesions was not observed. One patient (M V) developed a generalized pigmentation of the skin after taking large amounts of the drug for several months,

the continued administration of arsenic resulted only in very gradual intensification of the pigmentation

Serious bone marrow depression has occasionally occurred due to the arsphenamines but has been described only after the use of those arsenic preparations which contain the benzene ring. Aplastic anemia, agranulocytosis, and thrombocytopenic purpura are not mentioned either in the literature or in the pharmacologic texts, even as rare manifestations of inorganic arsenic poisoning. Hydrogen arsenide causes a severe anemia in both man and the experimental animal, but here the anemia is due to the markedly hemolytic action of this particular compound.³ Although there is apparently no danger of inducing bone marrow aplasia, the danger of other serious manifestations of arsenic poisoning must be continually kept in mind in giving, over long periods of time, the large doses of Fowler's solution necessary to induce symptomatic and hematologic remissions in leukemia. Unless frequent and careful clinical observations can be made, this form of therapy should not be used. The prolonged use of such a potentially dangerous drug, under the above conditions, is considered justified in view of the uniformly serious prognosis of the disease.

The mechanism of the action of solution of potassium arsenite in chronic myelogenous leukemia is not clear. Wichels and Hofer⁴ observed a reticulocyte response in normal individuals after the administration of toxic doses of the drug. Isaacs,⁵ working with white mice, concluded that arsenic solutions had a depressing effect on the bone marrow resulting in a decrease in the production of red blood cells. The effect of inorganic arsenic on the granulopoietic apparatus apparently has not been studied. The beneficial results observed in leukemia are apparently due in large measure to an inhibitory effect on the abnormal process of granulopoietic activity, resulting temporarily in a tendency for the involved structures to return to normal. This view is strengthened by the observation by Forkner and Scott¹ of return to red marrow in one patient in whom bone marrow biopsy was done after arsenic therapy. This inhibitory effect is apparently incomplete and temporary, symptomatic and hematologic relapse occurs after prolonged administration of the drug in adequate dosage. Further study of the effect of inorganic arsenic preparations on the blood and bone marrow of the human and of the experimental animal is needed.

Although roentgen therapy has been used in the treatment of several of the patients reported, conclusions as to the relative merits of roentgen and arsenic therapy are not justified. The number of cases is small, and in many instances less than the optimum amount of roentgen-ray therapy was given. However, the response in individual patients treated with Fowler's solution compares favorably with the reported symptomatic and hematologic response of patients adequately treated with roentgen therapy.⁶ This similarity in response of the patient with chronic myeloid leukemia to arsenic and to irradiation has been previously noted.¹ In considering the relative

merits of the two therapeutic procedures, several points should be borne in mind. Solution of potassium arsenite is relatively cheap, is readily available and does not require complicated and expensive equipment, or special technical experience on the part of the attending physician. Frequent clinical and hematological observations are essential, regardless of the method of therapy employed. While by no means all patients who receive roentgen-ray therapy have reactions, patients who have experienced both much prefer the repeated but usually mild symptoms of arsenic toxicity to the more severe and frequently incapacitating reactions which sometimes follow roentgen therapy. The alarming and frequently fatal bone marrow depression which may follow the irradiation therapy of chronic leukemia has not been reported in the small number of patients treated with Fowler's solution. A more extensive experience with the drug may reveal equally serious manifestations in unfavorable cases. It is apparent that arsenic is merely a palliative measure, with temporary effect, as is the case with roentgen therapy. However, an apparently effective agent is available for trial in those patients who become refractory to the effect of roentgen-rays. It is probable that arsenic may be most advantageously used in conjunction with or alternating with irradiation. Apparently the development of refractoriness to one or the other does not preclude the effective use of the alternative agent or a subsequent response to the original therapeutic measure. The question as to whether arsenic, used alone or in conjunction with irradiation, will appreciably prolong the life of the patient with chronic myeloid leukemia cannot be answered at the present time.

SUMMARY

1 Seven patients with chronic myelogenous leukemia, who have received one or more prolonged courses of solution of potassium arsenite, are described.

2 Solution of potassium arsenite is apparently an effective palliative agent in the treatment of chronic myelogenous leukemia.

3 In our experience, the drug is most effective if given in rapidly increasing doses until toxic symptoms appear and then continued in amounts as large as tolerated. Such a regime has been maintained for periods in excess of one year without serious reactions.

4 Solution of potassium arsenite administered in toxic or subtoxic doses to patients with chronic myelogenous leukemia usually results in (a) symptomatic improvement, (b) reduction in the size of the spleen, (c) decrease in the total white blood cell count, (d) decrease in the number of immature cells and in the number of nucleated red blood cells in the peripheral blood, (e) improvement in the anemia, (f) increase in platelets. Such evidences of improvement vary in degree and duration. Symptomatic and hematologic relapse may occur during the continued administration of the drug.

5 It appears that solution of potassium arsenite may be most advantageously used in the treatment of chronic myelogenous leukemia in conjunction with, or alternating with, courses of roentgen therapy

REFERENCES

- 1 FORKNER, C E, and SCOTT, T F M Arsenic as a therapeutic agent in chronic myelogenous leukemia, *Jr Am Med Assoc*, 1931, **iii**, 97
- 2 FORKNER, C E The administration of solution of potassium arsenite in the treatment of chronic myelogenous leukemia, *Med Clin N Am*, 1932, **xv**, 1057
- 3 FRITZWORT, F, HORWITZ, S, and ROSENBAUM, R Zur Frage der Arsenwasserstoffvergiftung mit besonderer Berücksichtigung der Blutveränderungen, *Ztschr f klin Med*, 1933, **cxxiii**, 703
- 4 WICHELS and HOFER, I Arsen und Blutbildung, *Klin Wchnschr*, 1933, **xii**, 591
- 5 ISAACS, R The effect of arsenic on the maturation of red blood cells, *Folia haemat*, 1928, **xxxvii**, 389
- 6 McALPIN, K R, GOLDEN, R, and EDSALL, K S The roentgen treatment of chronic leukemia, *Am Jr Roentgen*, 1931, **xxvi**, 47

ADOLESCENT DISTURBANCES OF ENDOCRINE FUNCTION, THE IMPORTANCE OF THEIR RECOGNITION AND TREATMENT^{*}

By CHARLES H. LAWRENCE, M.D., F.A.C.P., *Boston, Massachusetts*

It is manifestly impossible to discuss in a single article all the disturbances of endocrine function that may be encountered during the period of adolescence. I have, therefore, selected one type of dysfunction which is peculiarly related to that period, hypofunction of the anterior lobe of the pituitary gland.

It has long been known that the pituitary was a factor in the abnormalities of skeletal growth which are responsible for gigantism and dwarfism, but its responsibility for disturbances of maturation has been established more recently, and is still imperfectly understood. We have surmised that aberrations of that process were caused by functional disturbances of one or another of the endocrine glands, but have been unable until recently to identify the specific factors responsible for them. This fact, coupled with the observation that not a few of these disturbances of growth and development apparently corrected themselves completely by the time the age of maturity was reached, has resulted in our adopting an attitude of optimistic expectancy in regard to them. The ability of the individual to "outgrow" an adolescent arrest of development has been observed so frequently that it has been depended upon to meet the situation until its failure to do so was demonstrated after the growth impulse ceased. If the failure affects bodily growth markedly, its result is obvious, but if, as more commonly occurs, it results only, or chiefly, in incomplete maturity of the reproductive system, the condition often escapes notice, until symptoms referable to the genital organs direct attention to their incomplete development—too late, as a rule, to correct the defect.

Although no statistics are available concerning the frequency with which significant hypofunctional pituitary disturbances occur during adolescence, evidence is accumulating that they do so more often than has been realized, and that they are successfully "outgrown," or spontaneously normalized, less frequently than we have supposed, so that at present the physician finds himself in a dilemma when confronted by an adolescent patient with definite evidence of genital hypoplasia. Will the underlying pituitary hypofunction correct itself early enough and completely enough to achieve normal adult genital development, or does it require help, and if so, is effective help available?

In an effort to find the answer to these questions I have analyzed the records of two groups of patients. The first is composed of 97 couples

^{*} Presented before the General Sessions of the American College of Physicians, Detroit, March 5, 1936.

TABLE I
Genital Development and Endocrine Function
(97 Females)

	Endocrinopathy Present								*Adolescent Endocrinopathy Present function normal								Total Endocrinopathies
	T-	T+	P-	P+	G-	G+	A-	A+	T-	T+	P-	P+	G-	G+	A-	A+	
Genital Development																	
Normal (49 patients)	2	1	5	0	4	0	0	0	0	0	2	0	0	0	0	0	14 (28.5%)
Hypoplastic (44 patients)	1	0	22	0	11	0	0	0	0	0	10	0	0	0	0	0	44 (100%)
Undetermined (3 patients) †	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	2 (66.6%)
Atrophic (1 patient)	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (100%)

* Diagnosis from history and bodily configuration

† Measurements impossible because of pelvic tumors

The several foci involved are indicated by T for thyroid, P for pituitary, G for gonad, and A for adrenal The minus sign (-) indicates a depression of function, the plus sign (+) a hyperactivity

whose marriages were sterile, and in whom a complete study of the causes of sterility was made¹ From such a study some idea of the incidence of genital hypoplasia and the disturbances associated with it is obtained The second group is composed of patients who have been treated for hypofunction of the anterior pituitary lobe and the resulting genital hypoplasia, and offers evidence from which a working hypothesis concerning the value of treatment can be constructed

Table 1 shows the incidence of normal and hypoplastic genital development in the women of this series, and the association of existing or pre-existing endocrinopathies in the two subgroups The diagnosis of pelvic hypoplasia was made by vaginal examination and the determination of the uterine index by an independent observer¹ Among the patients with normal genital development there were 12 who showed clinical and laboratory evidence of co-existing endocrine disturbance, as contrasted with 34 women with genital hypoplasia who showed, by the same criteria, evidence of active endocrine disturbances In both groups, the anterior pituitary was the gland most frequently at fault, with ovarian hypofunction of the primary type, next Adolescent endocrine disturbances, which had spontaneously corrected themselves, were found in two patients with normal genital development, and in 10 with genital hypoplasia

A similar analysis of the males, using spermatogenesis as the criterion of normal gonadal development, is shown in table 2 Again the preponder-

TABLE II
Spermatogenesis and Endocrine Function in 97 Adult Males*

Spermatogenesis	T-	T+	P-	P+	G-	G+	A-	A+	Total Endocrine
Normal 34 pts	4	0	0	0	0	0	0	0	4 (11.7%)
Defective 63 pts	13	0	25	0	12†	0	0	0	50 (79.3%)

* The examinations of these patients were made by Dr S N Vose

† Six patients showed testicular hypoplasia Six showed cryptorchidism These conditions are probably the result of adolescent pituitary hypofunction, now compensated

ance of endocrinopathies, and in particular anterior pituitary hypofunction, in the group with defective spermatogenesis is striking, in contrast to their relatively low incidence in the group with normal gonadal function None of the normal group shows convincing evidence suggesting adolescent endocrine disturbance, while unmistakable stigmata of that condition, without metabolic disturbance at the time of examination, were found in 12 of the patients in the defective group The figures show a surprisingly high incidence of defective spermatogenesis among the males In part this may be due to an exacting standard of normality which included not only the number of spermatozoa, but their morphology, duration of motility, and percentage of abnormal forms as criteria However, the figures of Bland and

his associates,² which show more than 50 per cent of deficient spermatogenesis in the males of his series, agree essentially with ours in indicating that whatever the actual percentage may be, there is a very high incidence of defective spermatogenesis in males whose marriages are sterile. Such subnormal function, according to the work of Evans and his associates,³ is produced when the normal gonad stimulating hormone of the anterior pituitary is lacking, and its high incidence in these patients indicates a correspondingly frequent occurrence of hypofunctional pituitary disturbances, beginning probably during adolescence. The considerable number of patients with thyroid hypofunction serves as a warning, however, that pituitary hypofunction cannot be taken for granted whenever defective spermatogenesis is discovered.

Table 3 shows the incidence of normal and abnormal menstruation in the women composing our series. The correlation between normal genital development and normal menstruation, on the one hand, and genital hypoplasia and oligomenorrhea on the other, indicates that a definite relation between normal development and normal menstrual function exists, and that extremely short, scant, or infrequent menstrual periods are an indication of either genital hypoplasia or, in its absence, of ovarian pathology.

TABLE III
Genital Development and Menstrual Function in 97 Females (Sterile Marriages)

Genital Development	Menstruation Normal	Polymenorrhea	Oligomenorrhea	Dysmenorrhea
Normal (49 patients)	29 patients	1 patient	18 patients (7 = cystic ovaries) (1 = premenopausal)	1 patient
Hypoplastic (44 patients)	4 patients	4 patients	32 patients (2 = cystic ovaries) 1 patient	*13 patients
Atrophic (1 patient)	0 patients	0 patients		0 patients
Condition undetermined (organic pathology) (3 patients)	3 patients	0 patients	0 patients	0 patients

* Nine patients had both oligomenorrhea and dysmenorrhea.

There is at present some disagreement concerning what is normal menstruation. Boynton,⁴ King,⁵ and Allen⁶ have investigated the menstrual rhythm in healthy women, and have reached the conclusion that irregular menstruation is not uncommon among them, and Anspach and Hoffman⁷ have questioned the truth of the idea that most healthy women menstruate regularly and at 28 day intervals. Much of the significance of their findings depends upon what they mean by the word "health." It is obvious that perfect health, as the term is usually understood, can and does exist without complete development of the genital organs, and without their normal function. In our own series, none of the patients complained of ill health, nor

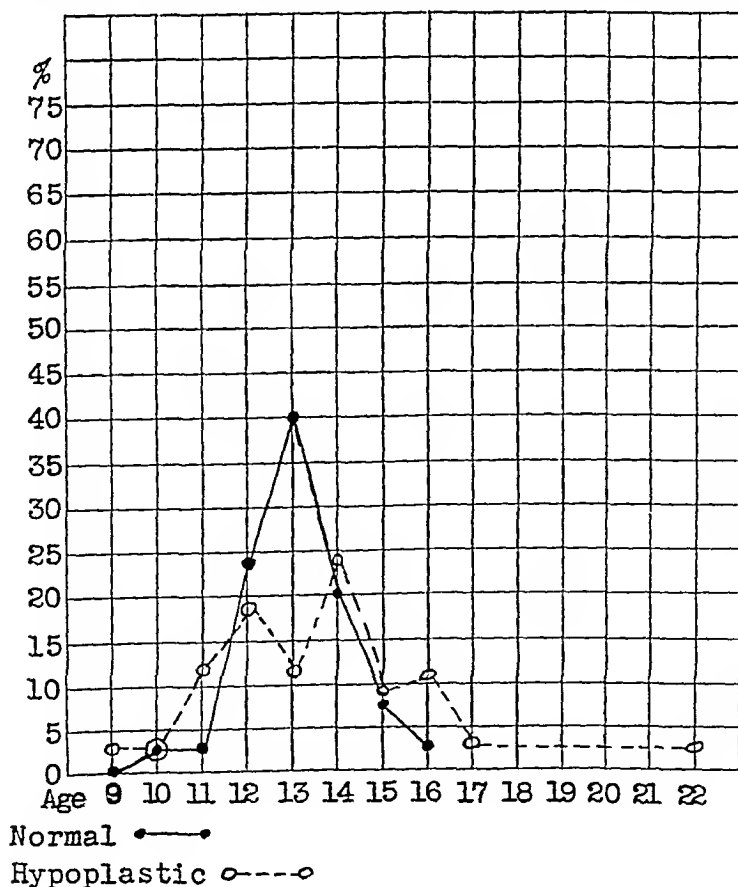
was organic disease, other than focal infection or moderate anemia, demonstrated in them, yet in those whose periods were abnormal by conventional standards, genital hypoplasia or polycystic ovaries existed in a significant majority. It is quite possible that undetected hypoplasia was the cause of the "abnormal" menstrual periods in the women investigated by the writers just cited.

In contrast to the differences of opinion concerning so-called normal menstruation, there is fairly general agreement concerning the normal age of menarche. Englemann⁸ in a study of 10,000 patients, found that the average age of menarche in American born women living in this country was 13.9 years. Meaker's¹ figures, from over 2,000 patients, show that menarche occurred in 80 per cent before the fifteenth birthday, so that it seems justifiable to regard the event as delayed when it takes place after that age has been reached.

An analysis of our own series (table 4) shows that there was a definite lag in the age of menarche in those patients who had reached adult life with-

TABLE IV

Age of Menarche in Patients with Normal and Hypoplastic Genital Development



out achieving complete sexual maturity. It likewise suggests that early menarche, before the eleventh year, does not insure normal developmental progress throughout adolescence.

The percentage figures for the "normal" group agree essentially with those given by Englemann⁸ and Meaker,¹ while those of the "hypoplastic group" show retardation of the onset of menstruation. From the point of view of diagnosis and treatment, it seems justifiable to conclude that if regular menstrual rhythm has not been established by the middle of the fourteenth year, an investigation of the patient's organic and metabolic condition is justified, and that if it is still absent at the beginning of her fifteenth year, appropriate treatment of the associated defect, again determined by careful and complete study, should be instituted if it is available.

In contrast to the female, the male exhibits no sharply defined events characteristic of adolescence which can be accurately timed. There is, however, some less dramatic evidence to indicate that similar retardation of development occurs in males. The most definite is delay or failure of testicular descent which, if it persists beyond the normal age of puberty, is generally believed to result in permanent depression or even total failure of spermatogenetic function. It is impossible to determine the incidence of cryptorchidism in civil life, but the records of the United States Army Medical Department⁹ showed that among the troops in the late war it occurred in three per thousand individuals. In our series of men whose marriages were sterile, it was found 12 times among 97 patients, associated with defective spermatogenesis in every instance.

From the evidence assembled in the foregoing analysis, it seems justifiable to draw certain conclusions, which if not completely proved, afford at least a fair working hypothesis for further investigation. These conclusions are: First, that in both males and females hypoplastic genital development is more common than has been supposed. Second, that such hypoplastic development is generally the result of a hypofunctional disturbance of the anterior pituitary gland, which in all probability begins during adolescence, and in the majority of individuals persists, if untreated, into adult years. Third, whether the pituitary hypofunction does so persist, or as may occur in a minority of cases normalizes spontaneously, the defect of genital development tends to be permanent throughout the reproductive period. It therefore, seems clear that treatment, if it is to be effective in preventing these developmental defects, should be applied before the end of the normal period of development.

There is, however, a lack of agreement concerning the value of treatment arising from the conflicting results of animal experimentation and clinical experience. Only lately has it become clear that many of these conflicts are due to species variations. These variations have been recently emphasized by Loeb and his associates¹⁰ who have shown that the effects observed in any experiment depend not only on the species of the test animal, but also

upon the species from which the extract employed was derived. It must be clear, therefore, that many of the apparently conflicting reports in the literature are not truly conflicting, since the experiments upon which they are based are not identical. It must also be equally clear that the effect of a given endocrine extract upon human beings cannot be accurately predicted from results observed in any other species. Such observations furnish the clinician with a general conception of the response to be expected, but its exact nature can be determined only by the study of patients before, during, and for a sufficient time after treatment to determine its permanent effect. Such studies are difficult to carry out in adolescent patients for obvious reasons. One cannot do vaginal examinations and endometrial biopsies, nor determine the uterine index, in adolescent girls, nor can one study the spermatogenetic function in adolescent boys. However, by using all the methods that can be fairly applied to each patient, it is possible gradually to accumulate a series in which the condition before treatment, and the response to it, can be established with reasonable certainty.

Table 5 shows the results of treatment in two groups of women so studied who exhibited, before treatment, definite evidence of anterior pituitary hypofunction and associated genital hypoplasia. The latter condition was determined by rectal pelvic examination in the adolescent patients, by

TABLE V
Results of Treatment

End Result	29 Adolescents		21 Adults	
	Amenorrhea	Menorrhagia	Amenorrhea	Menorrhagia
Well	71+%	62+%	30%	27+%
Mod improvement	14+%	0	10%	18+%
Slow improvement	0	0	10%	36+%
No improvement	14+%	37+%	50%	18+%

vaginal examination in the adults. The diagnosis of pituitary hypofunction was based upon history, physical examination, and metabolic studies. For convenience in tabulation, the patients have been grouped according to the type of menstrual disturbance which constituted their chief complaint. The term "end result" is used to indicate the condition existing six to 12 months after treatment had been omitted, and applies specifically to the menstrual disturbance and its associated genital hypoplasia. Each patient was treated with the same preparation of the anterior pituitary-like hormone derived from pregnancy urine*. The only variable factor was the duration of treat-

* The specific preparation used was Antutrin S (Parke, Davis Co.)

ment, which ranged between three and 12 months, according to the promptness of the response obtained

The number of patients on whom it has been possible to carry out these controlled observations is small, and hard and fast conclusions cannot be drawn from the series. The obvious difference in the results of treatment in the two groups, however, is larger than chance would account for, and suggests that the age factor may be an important one in determining the response. This idea receives support from observations on animals. Hertz and Hisaw¹¹ have shown that the female chinchilla rabbit four weeks old shows no response to a dosage of pituitary extract ample to elicit a maximal response in a rabbit of the same breed when 12 or 13 weeks old. Smith,¹² commenting on this fact, observes "From conditions found in women it may be surmised that after a certain degree of aging the reproductive organs lose their capacity to respond to the gonad stimulating hormone, for after the menopause, follicle stimulating hormone may be present in large amounts, yet reproductive cycles cease." "It is evident," he continues, "that the response elicited by injections of the pituitary or any other hormone is dependent on at least two factors—namely, the stimulating capacity or potency of the dosage given and the responsive capacity of the receptor tissue or organs." The results presented in table 5 suggest at least that the responsive capacity of the human ovary reaches its maximum during adolescence.

Just when this responsive capacity of the human gonads is initiated is not known, but certain clinical evidence shows that it is present, in some degree, before puberty, at least in the male. This evidence is derived from the treatment of cryptorchidism with pregnancy urine extract, concerning which there are numerous reports in the literature. Rubenstein¹³ has reported the results of treatment of a patient ten and a half years old who had dystrophia adiposo-genitalis and intra-abdominal testes. The left testis entered the inguinal canal and could be pushed into the scrotum after six injections, totalling 250 rat units. After five months' treatment it had descended completely, the right one partially, and both had increased in size. In contrast, Brosius¹⁴ reports no effect from similar treatment in a pituitary dwarf 38 years old. Dorff¹⁵ has recently published a careful study of 14 (?) male children with maldevelopment and maldescent of the testes. He calls attention to the fact that response is slow, but that it was most rapid in the patients who were close to puberty. Sexton¹⁶ has reported satisfactory response to treatment in a boy 18 years old with double cryptorchidism. It seems apparent from these results that the treatment of genital hypoplasia is about equally effective in both sexes, and that its effectiveness is influenced to a considerable degree by the age of the patient, reaching its maximum at or about puberty, and showing a decided diminution in adult life.

As a corollary, treatment for that condition should be begun in time to

take advantage of the capacity for response. Doing so may involve the occasional treatment of a patient who would have achieved normal development without help, but failure to do so means the acceptance of an unjustifiable handicap. I wish to emphasize again, however, my statement that treatment should not be instituted until a painstaking and complete study has identified the causative factor or factors responsible for the individual patient's developmental delay.

CONCLUSION

In conclusion, I wish to restate briefly the working hypothesis which seems to be justified by the evidence presented.

Genital hypoplasia, anatomical or physiological, is more common than is generally appreciated. It is caused, in the majority of individuals, by a functional depression of the activity of the anterior lobe of the hypophysis, developing during the pubertal or adolescent periods, but other possible causes, endocrine and non-endocrine, must be recognized. In the female, its existence is suggested by any significant abnormality of the menarche or menstrual rhythm, and can be proved by appropriate examinations. Its causative factors can also be demonstrated by careful study. In the male, the diagnosis is often more difficult to establish before adult age is reached except when physiological hypoplasia is accompanied by obvious anatomical stigmata.

Treatment, to be most effective, must be instituted during the pre-pubertal or adolescent period.

BIBLIOGRAPHY

- 1 MEAKFR, S. R. Human sterility, 1934, Williams and Wilkins Co., Baltimore.
- 2 BLAND, P. B., FIRST, A., and GOLDSTEIN, L. Clinical investigation of functional sterility in the female, *Jr Am Med Assoc*, 1935, cv, 1231-1237.
- 3 EVANS, H. M., PENCHARZ, R. I., and SIMPSON, M. E. Repair of the reproductive system of hypophysectomized female rats, *Endocrinology*, 1934, xxviii, 601-618.
- 4 BOYNTON, R. E. Study of menstrual histories of 2282 university women, *Am Jr Obst and Gynec*, 1932, xxiii, 516-524.
- 5 KING, J. L. Menstrual intervals, *Am Jr Obst and Gynec*, 1933, xxv, 583-587.
- 6 ALLEN, E. Irregularity of the menstrual function, *Am Jr Obst and Gynec*, 1933, xxv, 705-708.
- 7 ANSPACH, B. M., and HOFFMAN, J. Endometrial findings in functional menstrual disorders, *Am Jr Obst and Gynec*, 1934, xxviii, 473-481.
- 8 ENGLEMAN, Obstetrics and gynecology, Curtis, 1933, W. B. Saunders.
- 9 McKENNA, C. M., and EWERT, E. Management of undescended testicle, *Jr Am Med Assoc*, 1935, cv, 1172-1176.
- 10 LOEB, L., ANDERSON, W. C., SEXTON, J., HAYWARD, S. J., and KIPPEN, A. A. Experimental dissociation of the effects of anterior pituitary glands of various species on thyroid and ovary, *Science*, 1935, lxxxii, 331-333.

- 11 HIRTZ, R, and HISAW, F L Effects of follicle-stimulating and luteinizing pituitary extracts on the ovaries of the infantile and juvenile rabbit, *Am Jr Physiol*, 1934, *cvi*, 1213
- 12 SMITH, P E General physiology of anterior hypophysis, *Jr Am Med Assoc*, 1935, *civ*, 548-553 Hypophyseal gonadotropic hormones, *ibid*, *civ*, 553-559
- 13 RUBENSTEIN, H S The production of testicular descent with anterior pituitary-like fraction of pregnancy urine, *Endocrinology*, 1934, *xviii*, 475-481
- 14 BROSIUS, W L Clinical observations on the effect of APL (Antuitrin-S) on the testicle, *Endocrinology*, 1935, *xix*, 69-76
- 15 DORFF, G B Maldevelopment and maldescent of the testes, *Am Jr Dis Child*, 1935, *i*, 649-660
- 16 SEXTON, D L Treatment of sexual underdevelopment in the human male with anterior pituitary-like hormone, *Endocrinology*, 1934, *xviii*, 47-58

OXYGEN TREATMENT AND THYROID ABLATION IN THE TREATMENT OF HEART DISEASE ~

By ALVAN L. BARACH, M.D., F.A.C.P., DICKINSON W. RICHARDS, M.D.,
and W. BARCLAY PARSONS, M.D., *New York, N. Y.*

THE primary function of the lungs is to transmit to the arterial blood coursing through them an adequate supply of oxygen from the inhaled atmospheric air. During expiration carbon dioxide and water vapor are eliminated. The delivery to the tissues of the oxygen absorbed by the arterial blood is dependent upon the heart, the peripheral circulation, the amount of functioning hemoglobin, the blood volume and other factors. If the heart action is sufficiently impaired it is unable to maintain adequate blood flow, and the oxygen is supplied to the tissues at a tension less than that needed for proper functioning of the various organs in the body.

In this clinic, an attempt to treat heart failure was made by increasing the amount of oxygen carried by the arterial blood, through the inhalation of high oxygen atmospheres¹. An added increment of oxygen was provided for the arterial blood with less ventilatory effort, oxygen reached the tissues (including the heart) at higher tensions, oxygen transport was thus more effective, and in certain patients, circulatory compensation was thereby restored.

A more radical therapeutic measure than the provision of an increased arterial oxygen supply is the reduction of the oxygen requirement of the patient through total ablation of the thyroid gland (Blumgart, et al.²). In decreasing the needs of the body for oxygen by 25 to 35 per cent, the work required of the heart is so much less than it was that a slowed blood flow becomes adequate to the metabolic demands of the patient. It has, of course, been recognized that the full pursuits of life's activities may be threatened by such a marked reduction in oxygen consumption, approximately to two-thirds of the normal metabolism. The development of hypothyroid states of varying degree, however, is requisite for a significant decrease in the work of the heart.

In each type of therapeutic approach an adequate amount and tension of oxygen in the tissues of the organism are striven for.

Since we had employed oxygen treatment as a method of facilitating the recovery of patients with cardiac insufficiency, it seemed reasonable to extend it to the procedure of thyroidectomy in heart disease. Twelve patients with heart disease, in whom thyroid ablation was performed with the aid of oxygen treatment, will be presented in this communication.

* Received for publication February 17, 1936.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

HISTORICAL

The rationale for the removal of the thyroid gland which Blumgart and his collaborators have carried out in various types of heart failure was derived by them from investigations concerning the effect of the hypothyroid state on blood velocity.³ According to their reports, the blood velocity varies with the metabolic demands of the body, it is increased in hyperthyroidism and decreased in myxedema. In patients with congestive heart failure, the blood velocity was found to be considerably retarded, in general in proportion to the degree of failure, although the metabolic needs of the body were not lessened. By lowering the basal metabolic rate, i.e., by thyroidectomy, the work the circulation had to do was conspicuously lessened. Equilibrium between the metabolic rate and the blood velocity thus effected was found to restore compensation.

When thyroid ablation was contemplated in our clinic, we proposed to treat these cardiac patients with oxygen prior to operation for a period sufficient to remove as far as possible the signs of cardiac insufficiency, and to employ oxygen during the operation itself and for a period following it. The operative mortality in patients subjected to this operation in various clinics warranted in our minds not only a careful selection of cases but every aid that might be found to lessen the chances of death due to the operation. In a recent series reported by Blumgart et al.,⁴ of 50 cases of congestive heart failure, six patients died as a result of the operation. In 25 cases of angina pectoris, none died. In some of their severe cases, our suggestion of preoperative as well as postoperative oxygen treatment was adopted.⁵ Since the use of oxygen as an accessory to the procedure of thyroid ablation has appeared to result in a specially smooth postoperative course, so far without operative mortality, the basis for its employment will be reviewed.

It has long been known that the rate of normal heart is especially responsive to changes in the oxygen tension of the inspired air, slowing when pure oxygen is breathed and becoming regularly elevated when the atmosphere has either a diminished concentration or pressure of oxygen. In addition to an increased rate, dilatation of the heart occurs as a result of oxygen-want in normal men at high altitudes (Campbell⁶). In small animals Campbell reported degenerative changes in the myocardium as a result of prolonged exposure to low oxygen atmospheres.⁶ Katz and Long,⁷ using mammalian heart preparations, have shown that by reducing the oxygen supply to the heart there was rapid dilatation and failure of function, the contractions becoming progressively feebler and conduction slower. When the lactic acid accumulated, as a result of anoxemia, to 2.5 times the normal level, they found complete exhaustion took place, whereas skeletal muscle could withstand up to 4.5 times the normal level, revealing the greater intolerance of the heart to oxygen debt. In experiments on the effect of diphtheria toxin in circulatory failure, G. T. Evans⁸ found that the striking feature was sud-

den death and that this could be prevented by artificial pulmonary ventilation. When artificial pulmonary ventilation was not carried out, the heart was found to be almost completely depleted of glycogen. In other words, as Meakins⁹ has said, the sudden deaths appeared to be due to a respiratory failure with progressive anoxemia, producing a conspicuous reduction in cardiac glycogen. Under no conditions of severe physical exercise was it possible to lower cardiac glycogen below the normal levels, whereas marked anoxemia depleted cardiac glycogen within a minute or two. Animals breathing atmospheres containing 7 to 6 per cent oxygen gave up as much as two-thirds of their cardiac glycogen.

The heart, therefore, appears to be especially sensitive to oxygen-want. When it is failing it shows its dependence upon the amount of oxygen furnished to it by improving in its function when high concentrations of oxygen are inhaled. Beddard and Pembrey¹⁰ in 1908 observed that the inhalation of oxygen resulted in a decreased pulmonary ventilation in a patient with cardiac insufficiency, which was confirmed subsequently by Campbell, Hunt and Poulton¹¹ and by Barach and Richards^{1b, 1c}. Means and Newburgh¹² in 1915 found a diminished oxygen saturation of the venous blood in cases of cardiac decompensation. Harrop¹³ showed that a diminished arterial oxygen saturation was also frequently present. Barach and Woodwell¹⁴ administered 40 to 60 per cent oxygen to cases of cardiac insufficiency for short periods and observed an increase in the arterial saturation and a corresponding elevation of the venous oxygen saturation. In addition, they noticed a definite slowing of the pulse incident to inhalation of high oxygen atmospheres but did not discover alleviation of cardiac dyspnea, due to the brevity of the periods of oxygen administration and the use of a mask or mouthpiece.

In 1927 Campbell and Poulton¹⁵ reported beneficial effects of continuous residence in an oxygen chamber on subjects with dyspnea, especially when related to chronic bronchitis and emphysema, but including also one case of arteriosclerotic myocardial failure. Barach and Richards¹ (1930 to 1935) have presented investigations which reveal in a more detailed manner the special effects of oxygen treatment in congestive heart failure. Their results may be briefly reviewed as follows. Subjective improvement, relief of dyspnea and cough, begins generally in about three hours after entrance to the oxygen chamber and becomes well-marked on the following day. Between the third and sixth days of residence in a high oxygen environment, a diuresis sets in, in the favorable cases, which progresses until the patient is edema-free. This diuresis has been shown to be specifically dependent upon oxygen inhalation and not upon rest in bed, by withdrawal of oxygen in certain instances with cessation of diuresis and recurrence of edema. Objective changes are an increased oxygen saturation of the arterial blood, decreased pulse rate, lowered pulmonary ventilation, fall in blood lactic acid, gradual increase in vital capacity and a characteristic rise in the arterial CO_2 .

content The CO_2 curve of the arterial blood may increase from 50 to 100 per cent of the normal level as a response to inhalation of 50 per cent oxygen, representing a mechanism for the elimination of greater amounts of CO_2 in a decreased volume of breathing, which the provision of increased atmospheric oxygen makes possible This cardio-respiratory rest which oxygen therapy makes possible may be of significance not only as providing relief of symptoms but also as an important factor in the restoration of compensation When the lungs move more freely, as pulmonary congestion diminishes, the CO_2 curve falls, even in the presence of a high oxygen environment Deeper ventilation is then employed by the patient for CO_2 elimination rather than the shallow breathing which oxygen therapy makes possible when passive pulmonary congestion is present

The relief of dyspnea which oxygen therapy induces is sometimes almost immediate as in certain cases of Cheyne-Stokes breathing, sometimes delayed In a period of several hours, however, the patient will usually notice some relief The delay is probably due in part to the time required for readjustment of CO_2 level of the blood This has been discussed in a previous paper It is evident that a diminished oxygen saturation of the arterial or venous blood is not felt directly as the sensation of dyspnea through its nervous pathways The relief obtained by oxygen therapy is produced by lessening the effort requirement by enabling not only a lessened total pulmonary ventilation but a shallower type of breathing The lungs are less locally harassed, the respiratory musculature is relieved of some of its burdensome labored action Decreased dyspnea results Peabody and his co-workers¹⁶ emphasized the rôle of lung stiffening in congestive failure (the theory first put forward by von Basch¹⁷), also the reduction of vital capacity and the mechanical limitations of chest movement Recently, Harrison¹⁸ has presented elaborate investigations in support of the reflex cause of cardiac dyspnea, minimizing the importance of chemical factors He states "As regards the dyspnea produced by mild exertion in patients with congestive heart failure (1) It cannot be due to inability to increase the cardiac output (2) It cannot be due to diminished cerebral blood flow

(3) It is evident that the dyspnea of mild exertion is not related to alterations in the oxygen, carbon dioxide, or reaction of the blood, either arterial or venous" He later remarks that attacks of cardiac asthma, when unaccompanied by pulmonary edema, are not likely to be associated with abnormalities in the composition of the arterial blood, and relief of the attack occurs independently of the changes in the composition of the arterial blood

We would criticize the conclusions of Harrison on two grounds, one of fact and one of logic As to the first, in the tables presented by Harrison, purporting to show the lack of alteration in blood gases in cardiac asthma, one finds that the majority of patients showed a definite lowering of arterial oxygen saturation, sometimes as low as 86 per cent (see reference 17, pp 172-173)

On the ground of logic, we believe, as Harrison does, that the primary and immediate cause of the *sensation* of dyspnea, not only in cardiac cases, but in all other instances as well, is to be looked for in the nature of the proprioceptive impulses streaming into the central nervous system from the air passages, lungs and moving framework of the chest. The difficulty with Harrison's point of view, as we see it, is his failure to give due importance to the subject's *breathing requirement*, as distinct from his *breathing capacity*. It is in most instances just as effective, in relieving dyspnea, to reduce the breathing requirement, as it is to increase the breathing capacity. Reduction in breathing requirement, as abundantly shown by Campbell and Poulton, by Richards and Barach, and others, is just what is accomplished by oxygen inhalation in cases of congestive heart failure.

(a) Total ventilation is less

(b) Breathing is light and shallow, instead of relatively deep and labored

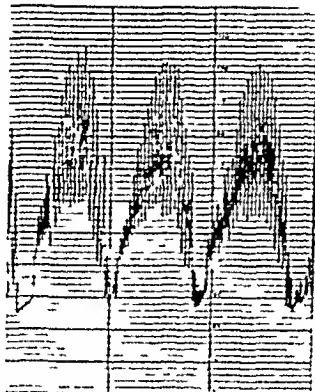
(c) Oxygen saturation of the arterial blood becomes normal or greater than normal

(d) Arterial CO_2 tension increases, but CO_2 combining capacity increases as well, and pH changes little

In the accompanying chart (chart 1), a patient with cardio-nephritic disease recorded his tidal volume while breathing air, 100 per cent oxygen, air again and 40 per cent oxygen. It can be seen that the relief of paroxysmal dyspnea, or cardiac asthma, took place immediately after the inhalation of oxygen and that the dyspnea recurred immediately when oxygen was withdrawn. In this case, there was no time for the pathology of the lung itself to change, the dyspnea was *chemically* relieved due to an alteration of the state of the blood gases in the patient which changed the type of respiration as well as decreased total ventilatory requirement.

There is an important aspect to this argument since it has been insufficiently recognized that oxygen therapy in heart disease is based on an actual need of the failing heart muscle for oxygen. In the investigations referred to by Richards and Barach,¹ clinical improvement in patients with congestive heart failure took place both in those in whom arterial anoxemia was present and to a degree in those in whom it was very slightly present or absent. Even without arterial anoxemia, many apparently compensated cardiac patients are in chronic oxygen debt (Uhlenbruck,¹⁹ Knipping²⁰), the measurement of which has been used as a criterion for oxygen therapy. There is therefore reason to believe that cardiac patients may make sufficiently severe efforts to cause distress in breathing in order to maintain their blood gases in a normal range, to fulfill oxygen requirement and be released from oxygen debt. Thus, one cannot conclude because the arterial oxygen saturation is normal or only slightly lowered that the threat of anoxemia is not burdensome to the patient.

MARKED AIR HUNGER
IN DYSPNEA



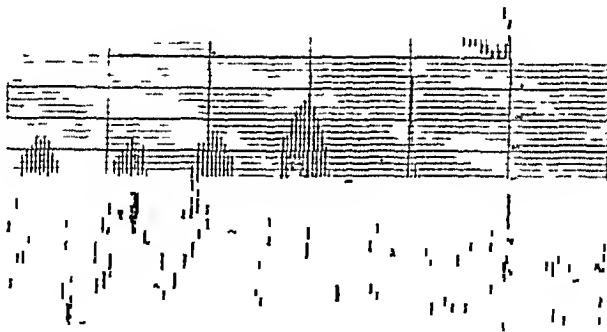
21% OXYGEN

COMPLETE SUBJECTIVE
RELIEF



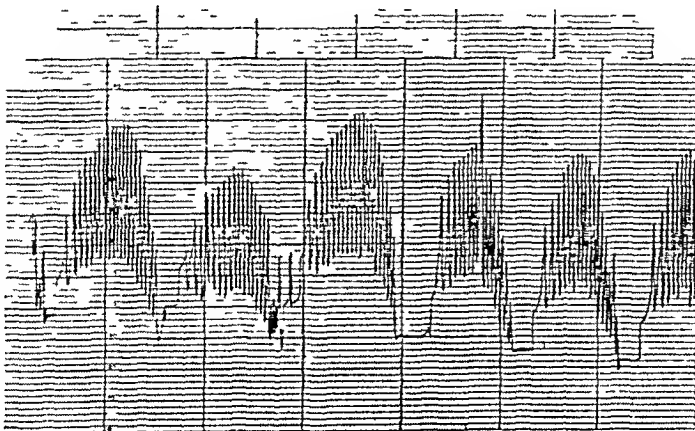
100% OXYGEN

RETURN OF
DYSPNEA IN
AIR



21% OXYGEN

GRADUAL
RELIEF OF
DYSPNEA



40% OXYGEN

CHART 1 Effect of Oxygen on Cheyne-Stokes Breathing

The effect of increased atmospheric oxygen is three-fold (1) The arterial blood contains an increase in the oxygen in physical solution and in that combined with hemoglobin, both of which afford a greater tension of oxygen and a greater delivery of oxygen per unit of blood flow. In other words, a diminished blood flow is made more efficient. In a converse way a small blood flow is made more efficient by a reduction of the oxygen consumption.² The second effect of increased atmospheric oxygen is an extension of the first, namely, that an increased delivery of oxygen per unit of blood flow supplies the heart muscle with increased oxygen, upon which it is peculiarly dependent, as noted above. A better contraction of the heart muscle in turn inaugurates a more efficient blood flow, and a virtuous cycle of increased oxygen supply replaces a vicious cycle of oxygen deficit, in which decreasing arterial oxygen tension makes for lessened ability of the heart to contract which in turn lessens blood flow, with an augmentation of the secondary results of cardiac failure, dyspnea and edema.³ In the third place, as indicated above, increased atmospheric oxygen enables pulmonary ventilation to proceed more efficiently and with actually less effort.

METHODS

When a patient was selected for thyroid ablation, he was transferred to the oxygen chamber, oxygen concentration 50 per cent. The chamber was of the thermal circulation type described by one of us.²¹ In cases of congestive failure, treatment was continued for two to three weeks or until evidence of decompensation receded. In patients with angina pectoris without congestive failure, a period of four to seven days of oxygen treatment generally preceded operation. The patient on the morning of operation was given a small dose of nembutal, 0.1 to 0.2 gm. A nasal catheter was inserted into the nasopharynx in the chamber and a flow of 5 liters of oxygen per minute begun before the door of the chamber was opened. He was then taken up the elevator and wheeled to the operating room without discontinuance of oxygen, the 220 cu. ft. tank being wheeled behind the patient. Oxygen was continued throughout the operation, which was done under local anesthesia, and the patient returned in a similar manner to the oxygen room. When the concentration was brought up to 50 per cent, the nasal catheter was withdrawn. Generally, a period of four days in the chamber followed, when the oxygen concentration was lowered to 40 per cent for 12 to 24 hours, then to 35 per cent for 12 to 24 hours, when he was removed to a ward or room. If lowering the oxygen concentration provoked too great a rise in pulse rate, i.e., over 10 beats per minute, the oxygen concentration in the chamber was elevated for two or three days and then again gradually lowered. If the patient had been withdrawn from the chamber, a nasal catheter was used for several days if the pulse became unduly increased.

The gas analysis was done by the method of Van Slyke and Neill. The blood volume was determined by the dye method, using brilliant vital red

(of Peters and Van Slyke) The venous pressure was measured by the direct method of Moitz and Tabora

RESULTS

Of 12 patients upon whom thyroid ablation was performed, five had rheumatic disease with congestive failure, two had arteriosclerotic disease with congestive failure, two had congestive failure with associated coronary sclerosis and anginal pain, and three had coronary arteriosclerosis with anginal pain without congestive failure. All the patients except one had a normal basal metabolism and experienced a complete ablation of the thyroid. One patient had hyperthyroidism with arteriosclerotic heart disease and congestive failure and was treated with oxygen and a partial thyroidectomy. In summary, nine of 12 cases had congestive heart failure prior to treatment.

CASE REPORTS

Case 1 N G, female, aged 34

Family History One daughter had rheumatic fever. *Personal History* No rheumatic fever but occasional sore throats as a child. Malaria at 14. *P I* Heart lesion first noted 17 years ago during first pregnancy. Six years ago, patient noticed dyspnea on climbing stairs, and for past five years has been practically incapacitated. During the last 18 months she has been confined to bed, with palpitation on the slightest exertion, intermittent edema and recurring ascites which finally necessitated paracentesis at three-week intervals.

Physical Examination A poorly developed, emaciated, cyanotic, adult woman, not dyspneic at rest. Neck veins dilated. Pupils react to light. Lungs contain râles at both bases. Heart enlarged in all diameters, systolic and diastolic murmurs at apex, blowing diastolic at the base, pulse totally irregular, exceptionally small volume. Blood pressure 80/40 mm of Hg. Abdomen distended with fluid. Liver hard, felt 7 cm below costal margin. Slight sacral edema without ankle edema.

Laboratory Findings Hgb 84 per cent, rbc 3.8 millions, wbc 4,600, polynuclears 83 per cent. Urine albumin, heavy trace. Serum protein 7.8 per cent. Electrocardiogram auricular fibrillation, R₂ and R₃ notched, T₁ diphasic, T₂ and T₃ inverted.

Course A paracentesis was done the day after admission with considerable relief. She was put in the oxygen chamber (concentration of oxygen 50 per cent), for two weeks when thyroid ablation was performed. A nasal catheter was inserted while the patient was in the chamber and 5 liters of oxygen administered during the transport of patient to and from the operating room and during the operation. Local anesthesia was used. The operation was performed without any signs of cardiac embarrassment. She was kept in the oxygen chamber for one week after operation, the oxygen concentration being gradually lowered the last three days, and then removed to the ward. As shown in chart 1, she had a slight increase in temperature with little change in her cardiac and pulse rates after operation. During the next 10 weeks, her basal metabolism gradually dropped from minus 13 to minus 43 per cent. Eight weeks after operation, she developed enough ascites to require tapping, 2,200 cc fluid were removed. She was discharged 14 weeks after operation, unmistakably improved, able to walk the length of the hospital floor without palpitation or dyspnea.

Before operation, her venous pressure varied between 130 and 153, after operation, between 135 and 225. Blood velocity before operation, 25-35, after, 38, 41, 48, 52 (table 1 and chart 2).

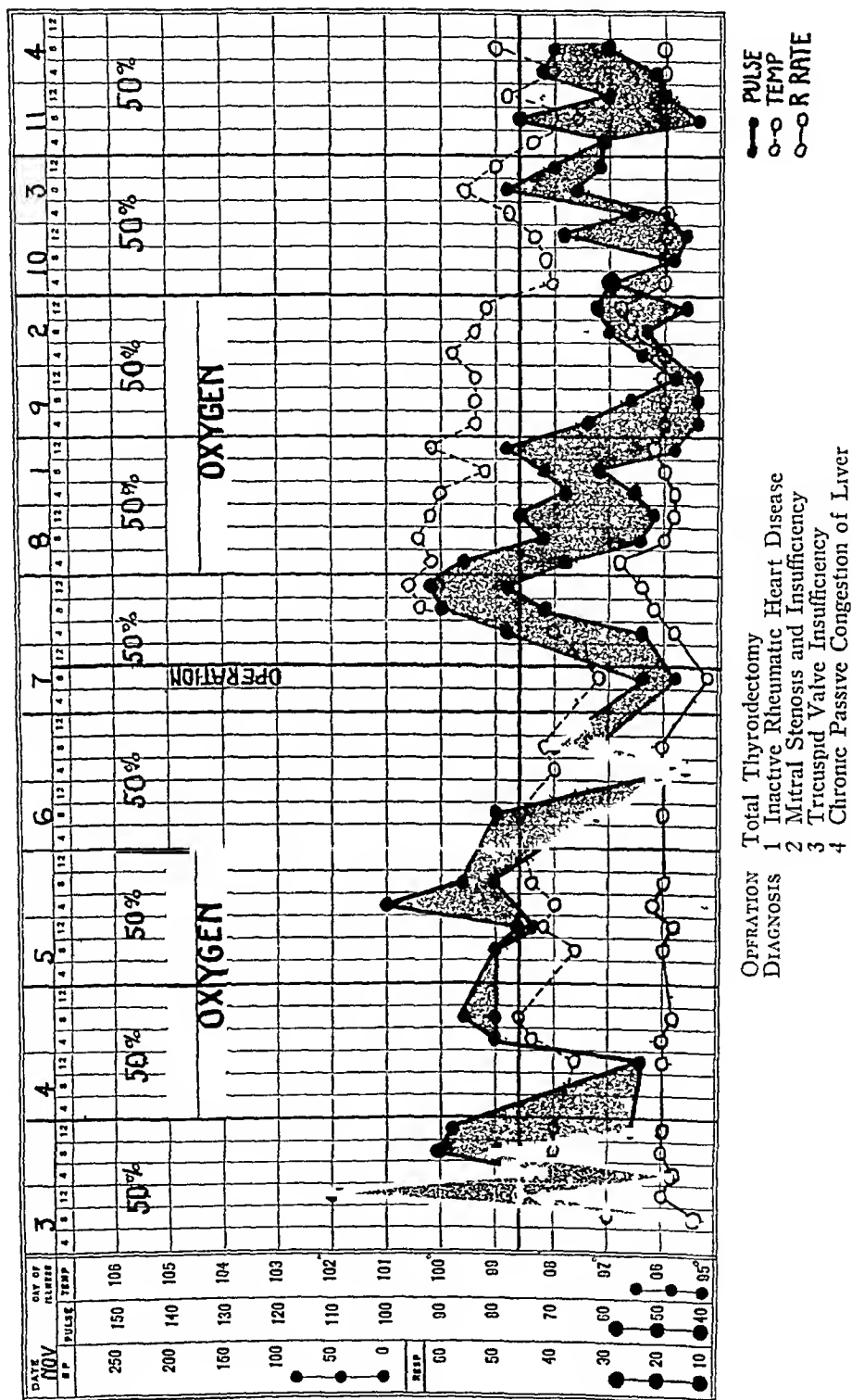


CHART 2 Clinical chart before and after thyroid ablation with patient in 50 per cent oxygen atmosphere

TABLE I

Case 1	Before Operation	After Operation	Remarks
Date	10-17-33 to 11-7-33	11-7-33 to 8-1-35	
Arterial oxygen saturation	94%	93%	Patient had been confined to bed for 18 months prior to operation. She was in oxygen chamber 14 days before and 6 days after operation. Arterial oxygen saturation in oxygen chamber 99 per cent. Ascites recurred for 1 year following operation. Since 10-17-34, no paracentesis necessary.
Hemoglobin	84%	72 to 85%	
Basal metabolism	-13	-18 to -43	
R B C millions per cu mm	3.8	3.6 to 4.2	
Vital capacity	900 to 1100	1200 to 1750	
Blood velocity (seconds)	25-35	38, 41, 48, 52	
Venous pressure	130-153	135 to 225	
Arterial pressure	100/60	95/50 to 120/70	
Sedimentation rate		45 mm / 1 hr	
Arterial CO ₂ vol per cent	53.6	55.4	
Blood cholesterol		194 to 205	
Wt kg	44	45.8	
Pulse	48-120	40 to 64	

Following her operation, December 7, 1933, patient was able to do more without heart consciousness or dyspnea than she had at any time during the previous five years. She required paracentesis at long intervals for one year and since that time has had no re-accumulation of fluid in her abdomen (from December 17, 1934, to the present time, December 7, 1935). She is up and about the house, does a small amount of shopping, walks in her garden, and has had no break in compensation. She has been kept on 0.1 gm digitalis daily. Her vital capacity before operation was between 900 and 1,100 c.c. Since operation, it has varied between 1,200 and 1,750 c.c. The electrocardiogram has not altered essentially. The blood velocity is slower, the venous pressure not appreciably different. The blood cholesterol reached a high of 205 mg per 100 c.c.

The patient was an intelligent Armenian, a writer, with marked emotional instability. For a year after operation, she believed that her writing was impaired by her lowered metabolism, this opinion being shared by an editor to whom she was accustomed to submit material. When her basal metabolism was raised to a level of minus 30 per cent she resumed her writing and the editor referred to said she wrote one of her best stories. It may also be said that her interest in her husband was revived as a result of her better physical health. She regards herself as having been strikingly benefited physically but believes she has been somewhat handicapped in her ability to write. She is on a maintenance dose of $\frac{1}{4}$ gr thyroid daily.

The follow-up results in this patient have been remarkably good. Bed-ridden for 18 months prior to operation, requiring paracenteses finally every three weeks,

conscious of her heart beat on the slightest movement, she became a woman able to carry on ambulatory activity without discomfort, being up five to eight hours daily. The signs of facial myxedema have been slight and the mental reaction to her operation has largely subsided. However, she has complained of pains in legs and feet for the past eight months. Noticeable crepitus on movement of the left knee-joint has appeared in the past four months.

Case 2 M M, female, aged 56

Personal History No rheumatic or luetic history. *P I* Ten years ago the patient was in the hospital for four months for cardiac insufficiency, she was discharged on digitalis, able to carry on ambulatory activity. Six weeks before the present admission, her abdomen began to swell, she became dyspneic and during the last three weeks before admission was confined to bed.

Physical Examination A slight, undernourished and pale cyanotic woman. Pitting edema over sacrum but not in legs. Lungs showed evidence of fluid at right base and moist râles over lower two-thirds of both lungs. Heart enlarged to left and right. Loud systolic and diastolic murmurs at apex. Heart fibrillating. Blood pressure 135/90 mm of Hg. Abdomen distended with fluid, and liver palpated below the umbilicus.

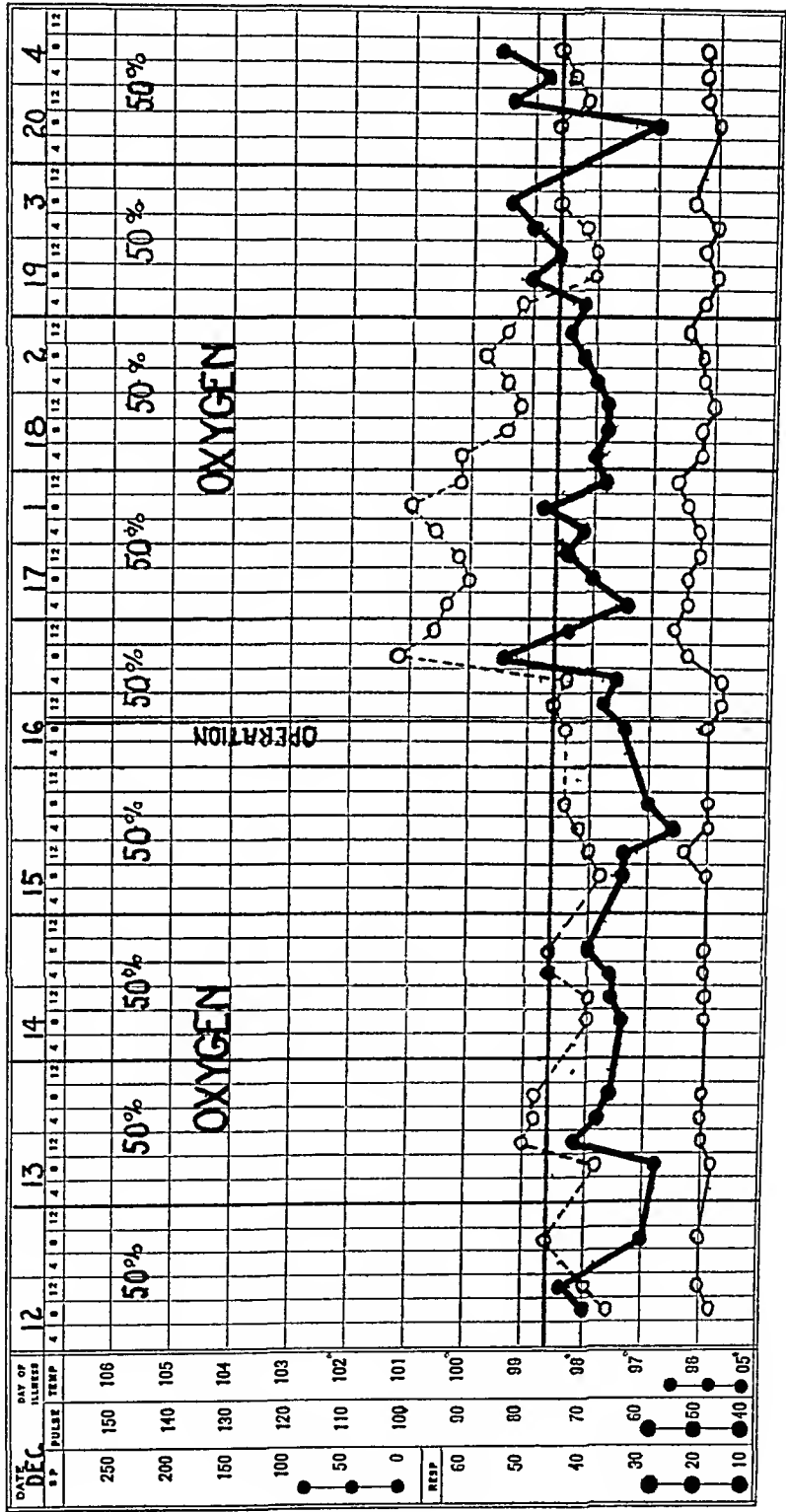
Laboratory Findings Hgb 82 per cent, rbc 4.2 millions, wbc 8,000, polynuclears 79 per cent. Serum protein 7.13 per cent. Electrocardiogram Auricular fibrillation, R_1 notched, T_1 inverted, T_2 and T_3 upright. Blood urea 32 mg per cent. *Course* After five months of routine hospital treatment, the patient was still bed-ridden, unable to regain sufficient compensation to be about in a chair. She was treated for three weeks in the oxygen chamber (oxygen concentration 50 per cent), and became free from dyspnea, orthopnea and heart consciousness. She was operated on while receiving oxygen through a nasal catheter, as outlined. She had scarcely any postoperative reaction (chart 3). She was removed from the chamber seven days after operation.

Basal metabolism dropped from minus 3 per cent before operation to minus 30 per cent one month later, finally falling to minus 42 per cent. Two months after operation the patient was able to walk slowly without dyspnea or heart consciousness. The liver was still palpable 8 cm below costal margin but there was no evidence of fluid or other sign of cardiac insufficiency. The venous pressure varied before operation from 260 to 53, after, from 175 to 57. The arterial oxygen saturation before operation was 93 per cent, after, 97 per cent. Vital capacity 1,375 before operation, after, 1,050 to 1,675 cc. Blood cholesterol increased to 264 mg per 100 cc blood. The blood volume was 4,600 before, 4,000 to 4,200 after operation (table 2).

The follow-up results in this patient were very good. She was able to go about, live in an apartment where she had to climb two flights of stairs, and felt comfortable and happy. Despite a basal metabolism that was approximately minus 40 per cent, she had little evidence of facial myxedema except an increased pallor and no distressing symptoms. Small doses of thyroid were given for a short time only, as they resulted in heart consciousness. She was nevertheless mentally alert. She was operated upon December 16, 1933. Except for a brief stay in the hospital in April 1935, for mild symptoms of cardiac insufficiency of five days' duration which quickly responded to rest in bed, she has been quite well. At the present writing (August 1935) she is ambulatory. Without thyroid medication her basal metabolism is minus 37 per cent.

Case 3 A S, female, aged 22

Personal History Patient had rheumatic fever with valvular heart lesion before age of ten. *P I* Four years ago, the patient developed symptoms of acute decompensation in the sixth month of pregnancy. After a rest period, Caesarian sec-



OPERATION
DIAGNOSIS

● PULSE
○ TEMP
○ R RATE

1 Total Thyroidectomy
2 Cardiac Insufficiency
3 Chronic Cardiac Valvular Disease
4 Mitral Stenosis and Insufficiency
5 Auricular Fibrillation
6 Cardiac Hypertrophy
7 Chronic Cardiac Dilatation
8 Posterior Poliomyelitis

CHART 3 Clinical chart before and after thyroid ablation with patient in 50 per cent oxygen atmosphere

TABLE II

Case 2	Before Operation	After Operation	Remarks
Date	7-3-33 to 12-16-33	12-16-33 to 8-1-35	
Arterial oxygen saturation	93%	97%	Oxygen treatment in chamber, 50 per cent oxygen, was carried out for 3 weeks. Patient lost sensation of dyspnea while in oxygen chamber and was generally improved. Liver was still much enlarged. No fluid in pleural cavities. Data before operation obtained in 3 separate admissions for congestive failure, dyspnea being outstanding symptom. Nasal oxygen, 5 liters per minute, was given during operation. She was in oxygen chamber for 7 days following operation.
Hemoglobin	73 to 86%	74 to 95%	
Basal metabolism	-3%	-20 to -42%	
R B C millions per cu mm	4 0 to 5 0	4 0 to 4 8	
Vital capacity	1375	1050 to 1675	
Blood volume	4600	4000 to 4200	
Blood velocity (seconds)	49, 43, 34	41, 52, 25 5	
Venous pressure	260 to 53	175 to 57	
Arterial pressure	104/60 to 150/100	145/70 to 108/65	
Sedimentation rate	20 mm /1 hr		
Arterial CO ₂ vol per cent	47 0	42 4	
Blood cholesterol mg per cent		264	
Wt kg	42 7 to 48 2	44 to 47	
Pulse	42	60	

tion and sterilization were performed. Since that time she has been admitted to the hospital five times for cardiac insufficiency. Her present attack began two weeks before this admission with edema of ankles, tachycardia, and dyspnea. Eight days ago, coughing and orthopnea appeared.

Physical Examination A well-developed girl with a hacking cough, without dyspnea or cyanosis. Lungs contain a few râles at the bases. Heart greatly enlarged. Rhythm totally irregular. Systolic thrill and double murmur at apex, diastolic murmur at aortic area. Blood pressure 160/70 mm of Hg. Liver palpable 7 cm below costal margin. Edema of feet, ankles and sacrum.

Laboratory Findings Hgb 85 per cent, rbc 4.5 millions, wbc 7,600, polynuclears 72 per cent. Electrocardiogram Auricular fibrillation, T₁ and T₂ upright, T₃ diphasic.

Course At the end of two months in the hospital, the patient was compensated in bed. She was treated in the oxygen chamber (oxygen concentration 50 per cent) for seven days prior to operation and eight days after under the usual technic. The operation was attended by a minimal reaction. Her basal metabolism, which was plus 6 to minus 10 before operation, was minus 13 per cent on discharge four weeks later, ultimately declining to minus 25 per cent. Vital capacity varied between 1,200 and 1,800 before operation, 1,300 after (table 3).

TABLE III

Case 3	Before Operation	After Operation	Remarks
Date	1-30-34 to 4-3-34	4-3-34 to 12-12-35	
Arterial oxygen saturation	95%	96%	Patient in oxygen chamber, 50 per cent oxygen, 7 days before operation and 8 days after operation. She had 5 admissions for cardiac insufficiency during previous 4 years
Hemoglobin	74 to 90	65 to 86	
Basal metabolism	+6 to -10	-13 to -25	
R B C millions per cu mm	3.8 to 4.8	2.8 to 4.7	
Vital capacity	1200 to 1800	1300	
Blood velocity (seconds)	25	35	
Venous pressure	28	45	
Arterial pressure	105/70 to 160/70	105/65	
Sedimentation rate mm /1 hr	16 to 57	58	
Arterial CO ₂ vol per cent	55.1	48.5	
Blood cholesterol		217	
Wt kg	47 to 49	55	
Pulse	80 to 84	82 to 92	

For three months after operation the patient did well, when palpitation, dyspnea and pain over her heart recurred. Symptoms persisted for seven weeks when she entered the hospital. At this time her hemoglobin was 66 per cent, r b c 2.8 millions with numerous macrocytes. During the nine weeks in the hospital thyroid was first administered and subsequently liver and iron, the hemoglobin rising to 81 per cent and the r b c to 4.0 millions. Six months after discharge, she said she felt "fine" on ambulatory activity. Her basal metabolism was then minus 13 per cent on 1 grain of thyroid daily. She took 0.1 gm digitalis daily.

Symptoms of cardiac insufficiency recurred seven months later, necessitating readmission to the hospital. However, her basal metabolism had become elevated to plus 5 per cent, which obviously counteracted the effect of thyroidectomy. After four months' hospitalization, during which time thyroid administration was stopped, the basal metabolism dropped to minus 20 per cent and she gradually regained compensation (December 1935).

Although the results in her case were complicated by high thyroid dosage, the amount of work she was capable of performing in her periods of compensation outside the hospital was greater than that she was able to do prior to operation.

Case 4 J. P., male, aged 51 years

Family History and Personal History Irrelevant. *P. I.* Patient began to have recurrent attacks of precordial pain radiating down left arm and dyspnea on exertion five years ago. Three years before the present admission he entered the hospital for alcohol injection. This resulted in a somewhat wider spacing of attacks but was followed by spinal pain and recurrence of anginal attacks. During this

period, he manifested considerable anxiety and depression, so that it was difficult to form a confident appraisal of the etiology of all his complaints

Physical Examination An obese, whispering, uncomfortable man sitting in bed, orthopneic and slightly cyanotic Pupils slightly irregular but reacted to light Heart greatly enlarged with P M I in sixth space, 15 cm from mid-sternum Sounds of poor quality Blood pressure 150/120 mm of Hg Radial artery thickened Lungs contained moist râles at both bases Abdomen Dullness in both flanks but no fluid wave or shifting dullness

Laboratory Findings Hgb 95 per cent, r b c 5 19 millions, w b c 8,600, polynuclears 75 per cent Urine, few granular casts Serum protein 7 per cent, non-protein nitrogen 36.4 Electrocardiogram sinus rhythm, R_1 , R_2 notched, T_1 , T_2 inverted, T_3 upright Indication of incomplete bundle branch block

Course After four weeks on the ward, thyroidectomy was performed He was in the oxygen chamber for eight days prior to operation and five days afterwards On removal from the chamber, he had a recurrence of chest pain, relieved by nasal catheter which was continued for three days His pain thereafter seemed to be definitely diminished However, the patient has done poorly Operated upon February 8, 1934, he was admitted twice during the following year, with slight congestive failure but mainly because of a depressed hopeless attitude He has spent all of his time in bed, both in the hospital and at home, complaining of weakness and recurrent chest pain Basal metabolism one year after operation was minus 28 per cent

It must be admitted that the operation did not justify itself in his case His anxiety state with persistent depression made it impossible to evaluate the results of the operation As seen in the table (table 4), the measurements recorded failed to give any evidence of improvement The venous pressure and blood volume tended to be higher after thyroidectomy, the arterial oxygen saturation only 1 per cent higher

TABLE IV

Case 4	Before Operation	After Operation	Remarks
Date	1-16-34 to 2-8-34	2-8-34 to 5-1-35	
Arterial oxygen saturation	92%	93%	Patient was in oxygen chamber 8 days before and 5 days after operation Recurrence of pain after removal from chamber was treated by nasal catheter for 3 days
Hemoglobin	103 to 113	85 to 115	
Basal metabolism	-2%	-14 to -27%	
R B C millions per cu mm	5.5 to 6.0	4.8 to 5.8	
Vital capacity	2400	2000 to 2700	
Blood volume	4144	5155	
Blood velocity		32 to 52	
Venous pressure	68	83 to 130	
Arterial pressure	152/100	136/92 to 178/128	
Arterial CO ₂ vol per cent	52.0	55.1	
Wt kg	73	72 to 74.3	
Pulse	80	74 to 80	

Case 5 W H, male, aged 51 years

Family History and Personal History Irrelevant *P I* For three years the patient has suffered from recurring, sharp, substernal and epigastric pain, radiating to back and down left arm, increasing steadily in severity and in the frequency of attacks. He had no orthopnea or ankle edema, but his illness prevented him from working for the past year and a half.

Physical Examination A well-developed pale man of 51. Fundi show slight narrowing of arteries. P M I 11.5 cm from midsternal line in fifth space. Sinus arrhythmia with numerous extra-systoles. Sounds distant. Soft, blowing systolic murmur at apex, loud rough systolic at aortic area. Radial arteries thickened. Blood pressure 145/90 mm of Hg. Liver edge felt 4 cm below costal margin.

Laboratory Findings Hgb 77 per cent, rbc 4.4 millions, wbc 6,100, polynuclears 67 per cent. Blood urea 46 mg per cent. Electrocardiogram. Ventricular premature beats, R_s notched, T inverted in all leads.

Course Patient was treated with 50 per cent oxygen in the oxygen chamber for nine days prior to operation and for 16 days after. The length of the postoperative oxygen treatment was due to the fact that the first attempt at lowering the oxygen concentration, on the fourth to the fifth day after the operation, was followed by rise in the pulse rate and recurrence of substernal pain. The second lowering of the oxygen concentration was uneventful. The operation resulted in a minimal reaction (chart 4 and table 5).

TABLE V

Case 5	Before Operation	After Operation	Remarks
Date	4-14-34 to 4-28-34	4-28-34 to 6-29-34	
Arterial oxygen saturation	96%	97%	Patient was in oxygen chamber 9 days before and 16 days after operation. First attempt at lowering oxygen concentration precipitated rise in pulse rate and recurrence of pain in chest, which was promptly relieved by raising oxygen concentration again to 50 per cent. Second lowering of oxygen concentration was borne without symptoms.
Hemoglobin	77 to 85%	83 to 85%	
Basal metabolism	+24%	-2 to -20%	
R B C millions per cu mm	4.5	4.1 to 4.7	
Vital capacity	2950	2500 to 2850	
Blood volume	5700	5000	
Blood velocity	25	25	
Venous pressure	10	25	
Arterial pressure	140/95	138/88 to 152/90	
Arterial CO ₂ vol per cent	48	55.3	
Pulse	108	68 to 100	

Before operation his basal metabolism was plus 24 per cent, during the five weeks after operation, his lowest basal metabolism was minus 11 per cent. During the last week he began to show improvement, with practically no discomfort on walking the hospital corridor. For one month after leaving the hospital, the patient did well, being able to walk 10 blocks without pain. Symptoms then returned worse than ever, and he reentered the hospital seven weeks after discharge. On this admission, his

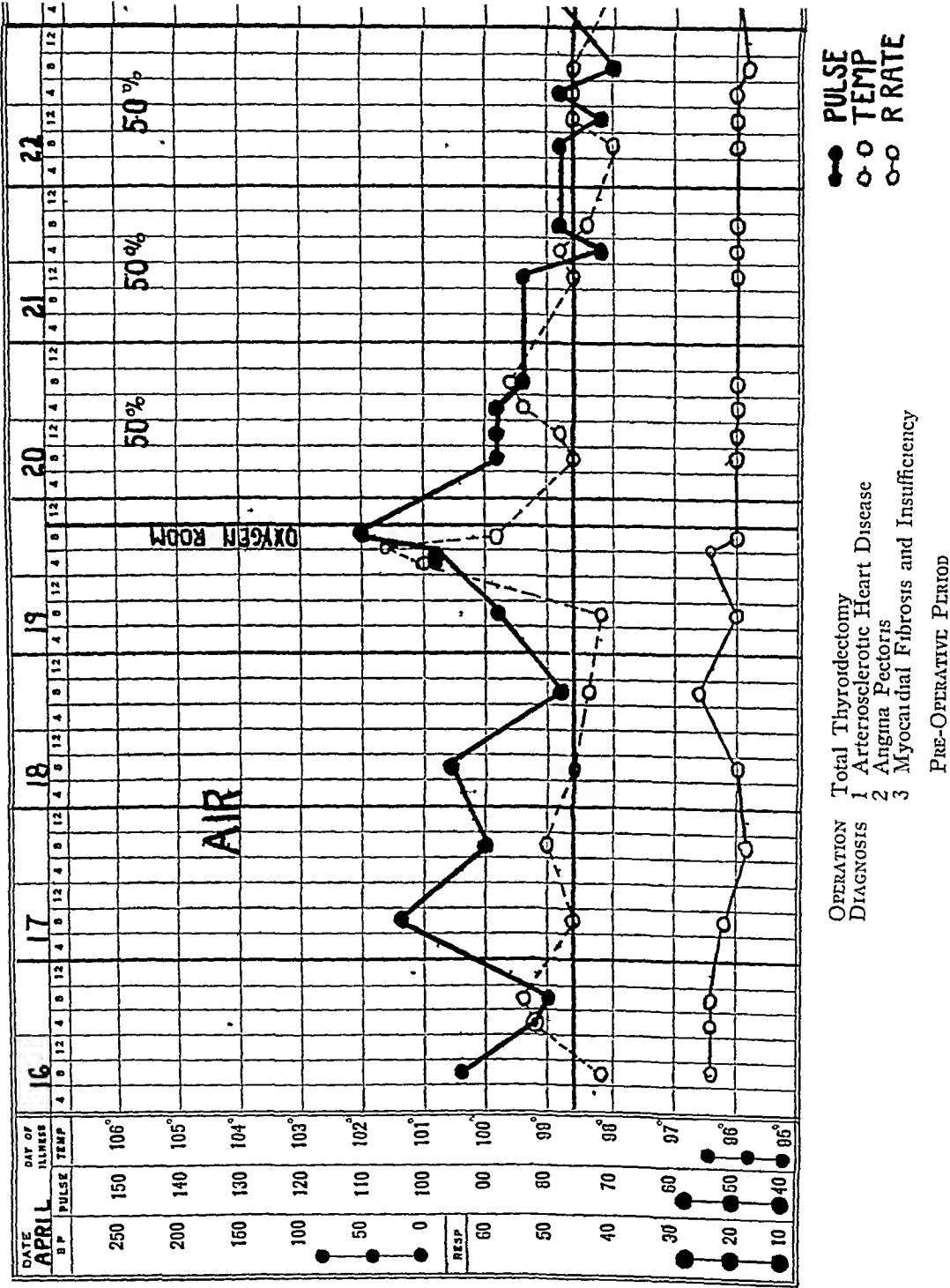
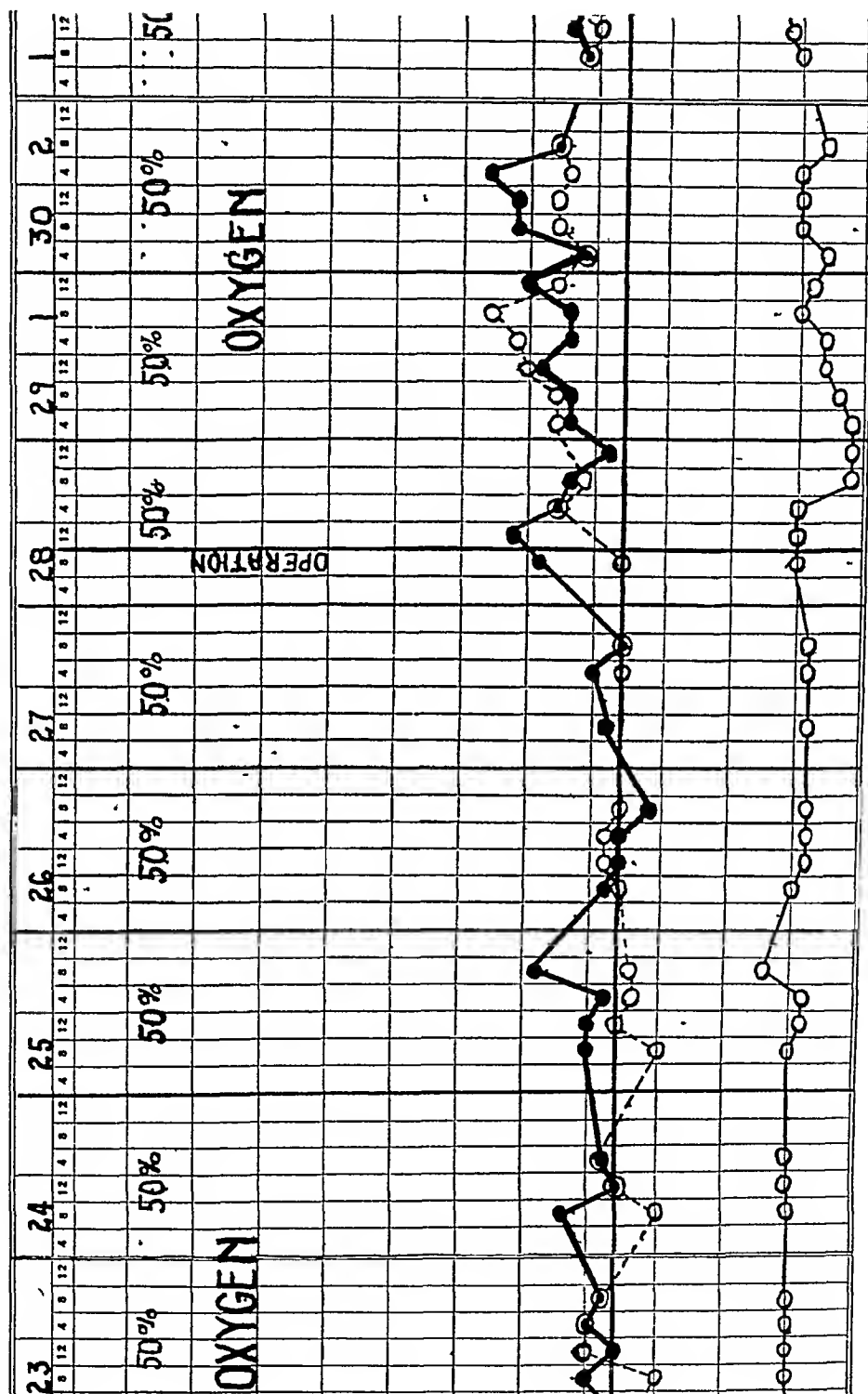
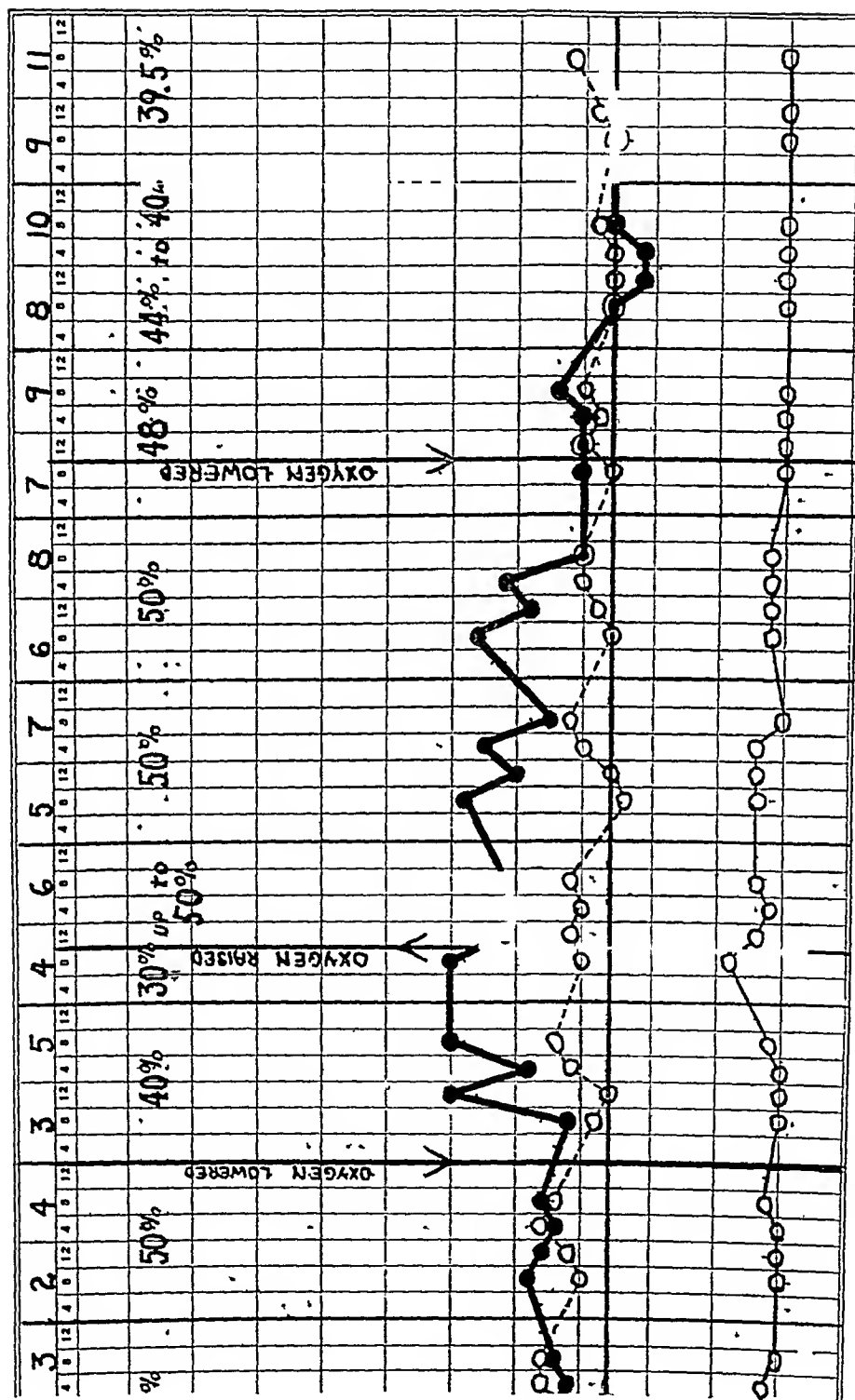


CHART 4 Clinical chart showing reduction of pulse rate due to oxygen treatment, minimal postoperative reaction and elevation of pulse on first attempt to lower oxygen concentration



OPERATIVE PERIOD
CHART 4—Continued



POST-OPERATIVE PERIOD
 CHART 4—Continued

blood count was lower, Hgb 70 per cent, rbc 3.5 millions. The electrocardiogram showed definite changes, the T waves in Leads I and II were more deeply inverted, T_1 diphasic, R_2 more notched. Blood cholesterol 208 mg per 100 cc. The lowest basal metabolism obtained was minus 20 per cent. Radiotherapy to the thyroid gland was begun. Four weeks after admission he began to have severe precordial pain at rest, unrelieved by nitroglycerine. His heart sounds became weak and he was placed in an oxygen tent, oxygen concentration 60 per cent. The next day he felt fairly well when suddenly he had a severe precordial pain and died almost instantly.

It was evident that thyroidectomy did not alter the progressive course of coronary sclerosis in this patient. Such improvement as took place was very temporary. At autopsy, a small nodule of hyperplastic thyroid was found, which accounted for the basal metabolism not reaching lower levels. However, since his preoperative reading was plus 24 per cent, a relative lowering of oxygen consumption did take place. Post-mortem examination revealed marked aortic stenosis with slight generalized coronary sclerosis.

Case 6 S S, male aged 57 years

Personal History Four years ago, the patient developed difficulties in urinating, and was treated two years later by supra-pubic prostatectomy. *P I* Three years ago, he began to be short of breath on exertion. Five months ago, he developed precordial pain on exertion. For four months he has suffered intermittent claudication in the legs. Three and one-half months ago, he went to bed for six weeks because of dyspnea and edema. Precordial oppression has frequently occurred while at rest, walking three blocks brought on pain in chest.

Physical Examination A plethoric, well-developed man of 57, somewhat orthopneic and dyspneic. Slight arterial tortuosity noted in fundi. Lungs, sibilant râles scattered throughout, with slight dullness at left base. Heart slightly enlarged. Systolic blow at apex. Radial artery sclerotic. No pulsation in dorsalis pedis or posterior tibial arteries. Blood pressure 160/90 mm of Hg. Varicose veins of legs. Liver edge palpable 3 cm below costal margin.

Course He was placed in an oxygen tent (oxygen concentration 50 per cent) and five hours later precordial oppression subsided. During a week in 50 per cent oxygen he had two minor attacks of upper precordial pain. On discharge his liver was not palpable and his lungs were clear.

One year later he was again admitted. In the intervening year symptoms of precordial pain had continued, brought on by walking one block, accompanied by dyspnea during the preceding three months. Lungs contained subcrepitant râles at both bases. The electrocardiogram now showed auricular fibrillation, T_1 and T_2 upright, S_3 notched. Heart little changed from previous admission. Blood pressure 170/100 mm of Hg. Liver 3 cm below costal margin. Blood urea 51 mg per 100 cc. He was kept in the oxygen chamber for one week prior to operation and six days after. His postoperative course after thyroidectomy was uneventful. His heart rate returned to sinus rhythm. He returned home three weeks after operation free from pain on mild exercise. Seven months later his electrocardiogram showed sinus rhythm, P_2 notched, S_2 notched, S_3 notched, T_1 and T_2 inverted and T_3 upright. Since the record taken on the previous admission, the T waves in Leads I and II had increased in amplitude and T_3 had become inverted.

His clinical course was characterized by severe facial myxedema which was uncomfortable enough for the patient to require thyroid extract, gr $\frac{3}{4}$ daily. When the thyroid dosage was raised to 1 grain daily, walking 15 blocks precipitated an attack of precordial pain for which he went to bed for two days. On his present dose of $\frac{3}{4}$ gr thyroid daily, he is able to walk 15 to 20 blocks without pain or dyspnea 16 months after operation. He does not feel strong enough to work. On limited ambulatory activity, he is comfortable. His face appears mildly swollen but

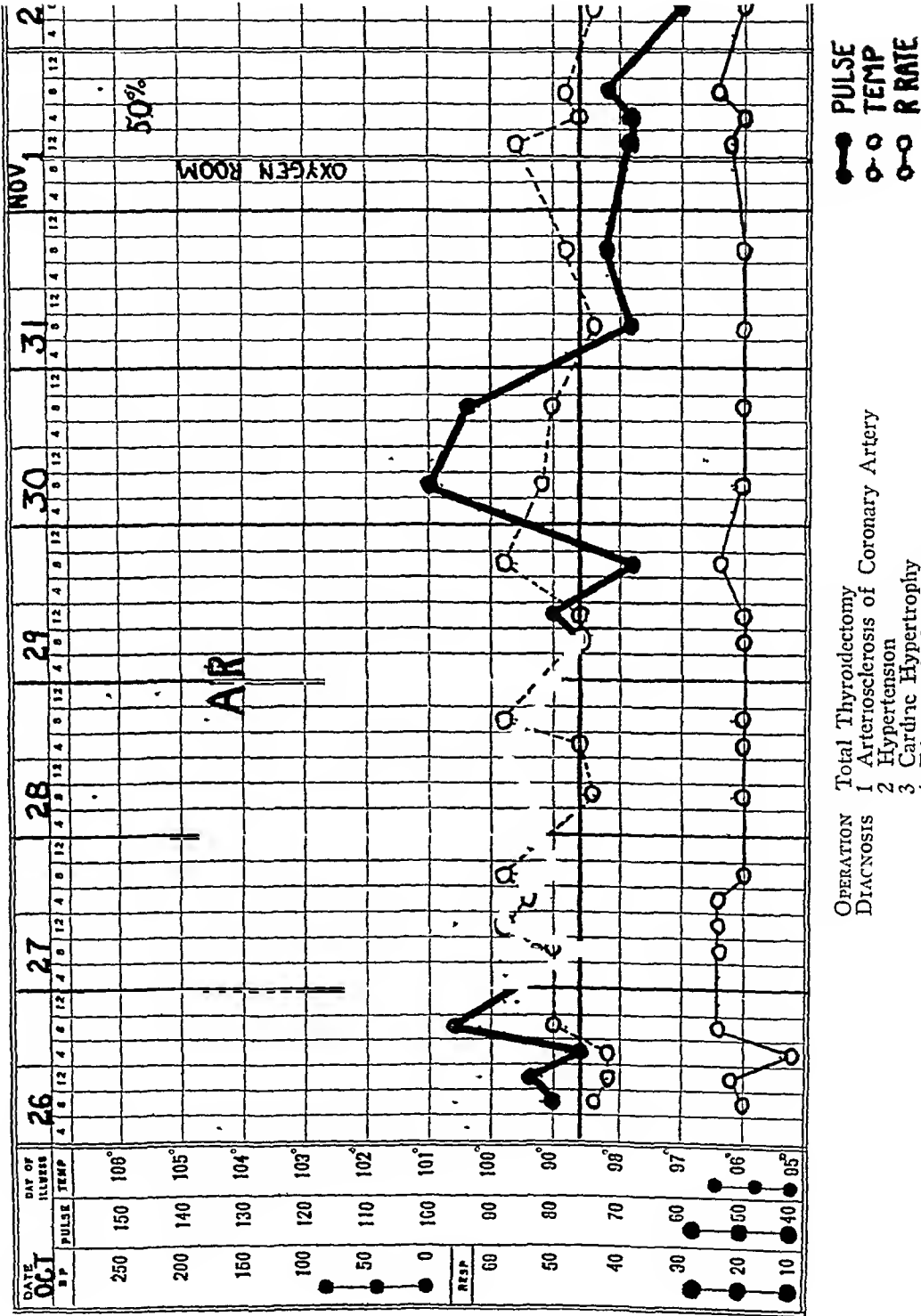


CHART 5 Clinical chart showing reduction of pulse rate due to oxygen treatment and elevation of pulse when oxygen was withdrawn

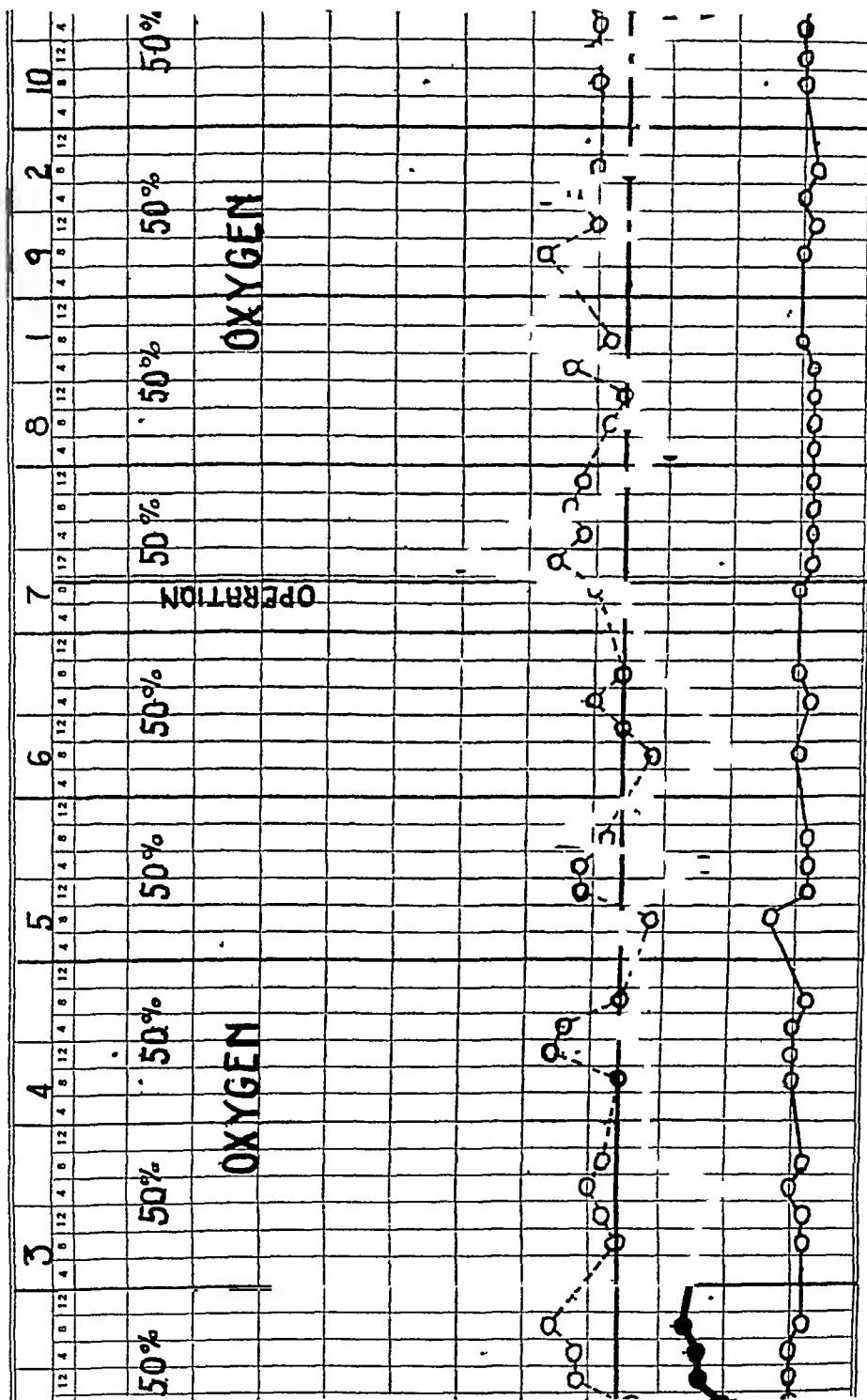


CHART 5—Continued

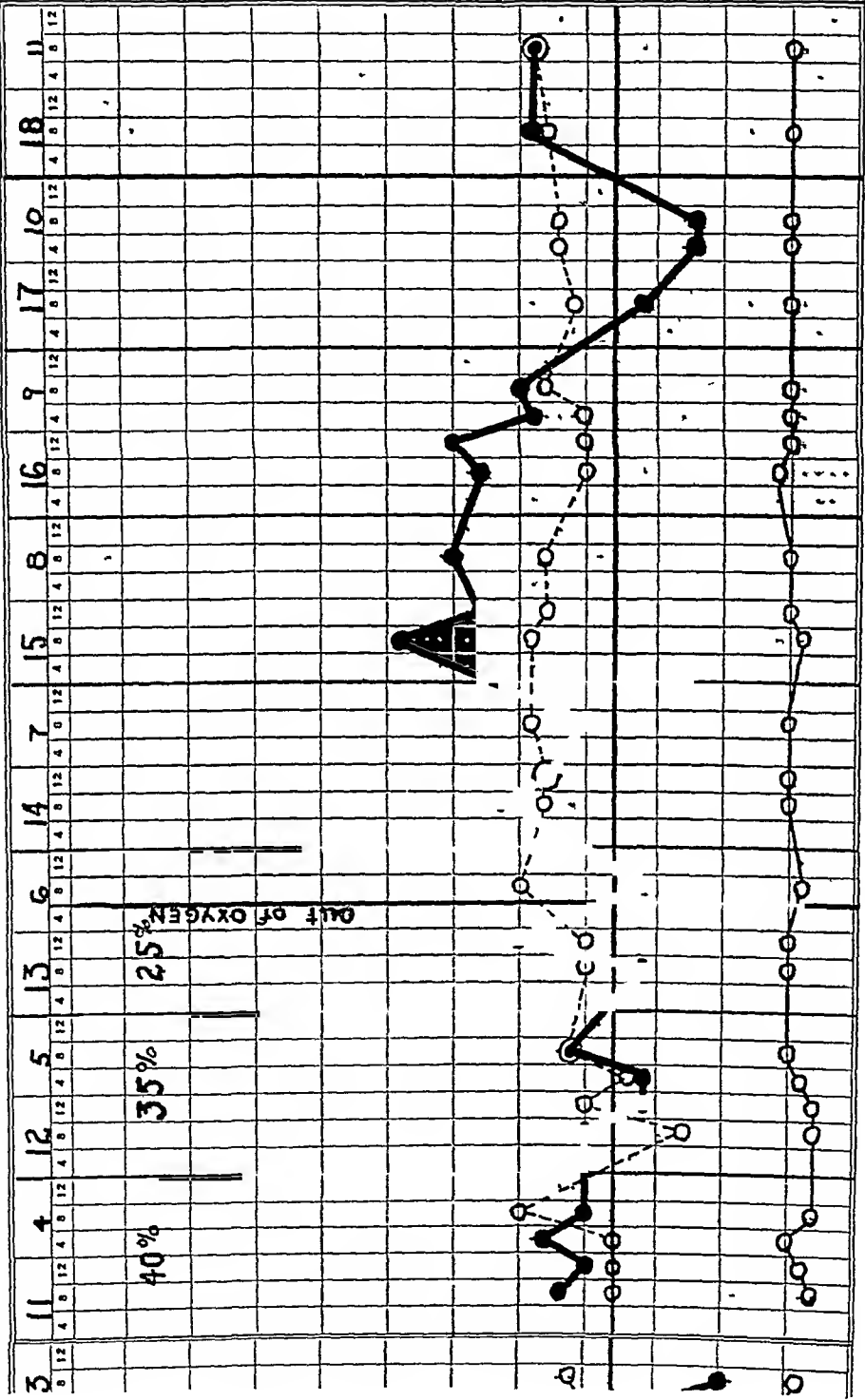


CHART 5—Continued

does not distress him. His blood pressure during the first two months after the operation was lower, 145/70 mm of Hg, but since then it has gradually become more elevated, from 195/125 to 200/130 mm of Hg. The laboratory data shown in table 6 reveal a slight increase in vital capacity, from 2,000 to 2,650 c c. The basal metabolism has been kept mainly at minus 35 per cent.

TABLE VI

Case 6	Before Operation	After Operation	Remarks
Date	8-9-34 to 8-21-34	8-21-34 to 10-1-35	
Arterial oxygen saturation	95%	98%	Patient was in oxygen chamber 7 days before and 6 days after operation
Hemoglobin	118		
Basal metabolism	+3%	-22 to -35%	
R B C millions per cu mm	6.8		
Vital capacity	2000	2650	
Blood volume	6180	6780	
Blood velocity	19	11	
Venous pressure	12		
Arterial pressure	180/100	136/58 to 200/130	
Arterial CO ₂ vol per cent	55.2	50.6	
Blood cholesterol		250	
Wt kg	66.8	66.4	
Pulse	72	44 to 80	

The patient feels much improved. He is quite philosophic about his inability to work, being content with a life of mild activity, supported by his son. The elevation of his blood pressure, particularly the diastolic, indicates that thyroidectomy has not arrested a pathologic circulatory process. On the other hand, it has made possible a comfortable existence. As a by-product of the operation, the symptoms of intermittent claudication have disappeared.

Case 7. Female, 43 years old

Past History. Irrelevant. *P. I.* Patient was well until six months ago when she began to have cough and shortness of breath on exertion. Her symptoms increased until she was confined to bed, one month after the onset of symptoms. In spite of digitalis and complete bed rest, she became progressively worse. Weakness and dyspnea continued with attacks of nocturnal dyspnea for which morphine was used. After four weeks of bed rest she was removed to the hospital and placed in the oxygen room at an oxygen concentration of 50 per cent.

Physical Examination. She was a chronically ill-looking woman sitting propped up in bed, pale without discernible cyanosis. Neck veins were moderately distended. There were dullness and diminished breath sounds and fremitus over the right lower lobe. Heart was enlarged 13 cm to the left and 5 cm to the right. A systolic murmur was heard at the apex. There were frequent premature beats. Blood pressure

130/80 mm of Hg The liver could be percussed as far as the umbilicus There was pitting edema over the sacrum and ankles

Laboratory Findings Hgb 90 per cent, rbc 4,500,000, wbc 7,400, polynuclears 76 per cent Blood NPN 35 mg per cent Electrocardiogram showed sinus rhythm, ventricular premature beats, P-R interval 0.16 sec, left preponderance, P notched in all leads, T_1 and T_2 inverted, T_3 upright Urine showed a heavy trace of albumin with an occasional hyaline cast Venous pressure 135

Course After entrance to the oxygen chamber the patient had no more attacks of paroxysmal dyspnea, and while at rest breathing was comfortable She was kept in the oxygen room for three and one-half weeks and then put on nasal oxygen for 10 days This was gradually reduced from five to one liter per minute before it was discontinued She lost approximately 15 pounds of edema She was allowed home and for a period of two months pursued mild ambulatory activities Then orthopnea, indigestion and slight shortness of breath recurred and she was admitted to the hospital to the oxygen room as a preparation for thyroidectomy Her vital capacity was 2,000 cc Basal metabolism plus 19 per cent Blood cholesterol 177 mg per cent Venous pressure 135 Blood pressure 140/100 mm of Hg On examination she had dullness and diminished breath sounds over the right lower lobe and pitting edema over the sacrum At the end of one week she was again entirely comfortable She was kept in the chamber for two more weeks, and after she was entirely free from symptoms of decompensation, she was operated on under nasal oxygen and returned to the chamber for one week She was given oxygen through nasal catheter for one more week, and left the hospital two weeks later She had a minimal postoperative reaction

Vital capacity on discharge was 2,800 cc Basal metabolism plus 1 per cent four and one-half weeks after operation and minus 8 per cent six months after operation Venous pressure before discharge, 45

This patient on her first admission showed a striking improvement on transfer to the oxygen chamber, especially characterized by prompt disappearance of paroxysmal dyspnea That improvement was not longer maintained seemed unusual in a case of arteriosclerotic heart disease When she was again put in the oxygen chamber, compensation was rapidly regained In the six months that have elapsed since operation, she has been very comfortable on mild activity, and says she feels like a new woman She has appeared definitely to benefit from the thyroidectomy, although the basal metabolism has only been reduced from plus 19 per cent to minus 8 per cent

An abductor paralysis of both vocal cords has, however, given her a husky voice which has persisted since operation

Case 8 Female, aged 46

Family History Two members of the family have had rheumatism *Personal History* Irrelevant *P I* At age of 33 the patient had her first attack of rheumatism Six years later she had a second attack at which time she developed cardiac symptoms For the past three years she has had shortness of breath, orthopnea, rapidly recurring ascites, finally requiring paracentesis every few weeks, frequent hydrothorax and persistent ankle edema

Physical Examination A chronically ill negress with edema of ankles and sacrum Chest shows right hydrothorax and moist râles at both bases Heart is markedly enlarged both to right and left with signs of mitral stenosis and insufficiency and aortic and tricuspid insufficiency Blood pressure 120/60 mm of Hg Abdomen distended with fluid Liver down 4 cm below costal margin

Laboratory Findings Hgb 92 per cent, rbc 5 millions, wbc 8,900, polynuclears, 62 per cent Venous pressure 278 Vital capacity 750 Serum protein 63 per cent NPN 32 mg per cent Electrocardiogram shows auricular fibrillation, left preponderance, R_1 and R_2 notched, T_1 and T_2 isoelectric, T_3 upright

Course She was put in the oxygen chamber for one week prior to operation and for three days after operation. She had a minimal postoperative reaction. Basal metabolism plus 5 per cent before operation, minus 23 per cent 23 days after operation, minus 35 per cent eight months after operation. Venous pressure 278 on admission, and 158 twenty-three days after operation. During the following eight months the patient has felt better and able to do definitely more than formerly, but recurring ascites has required paracenteses at intervals of 10 days to three weeks.

Case 9 Male, 60 years old

Past History Spontaneous pneumothorax 18 years ago. Questionable history of coronary occlusion 12 years ago. *P I* Hypertension discovered 10 years ago. Four years later he began to have paroxysmal difficulty in breathing at night, gradually increasing in frequency and severity. Three months ago patient had a severe attack of nocturnal dyspnea, and examination at that time showed definite heart failure. Apex rate 90, blood pressure 170/100 mm of Hg, many premature beats. Liver palpable below the costal margin. Lungs showed moist râles at both bases. Two months ago dyspnea increased, and he complained of severe pain in the left arm. Electrocardiogram showed right bundle branch block, marked slurring and notching of QRS complexes, diphasic T waves and many premature ventricular beats. Blood urea 62 mg per cent. Basal metabolic rate plus 12.

Physical Examination The patient showed marked dyspnea, at times gasping. His breathing was distinctly more comfortable while he was in the oxygen chamber (oxygen concentration 50 per cent). He spent 19 days in the chamber, and for 11 days after this was given oxygen by nasal catheter. Thoracenteses were repeatedly necessary, 1,800 c.c. of fluid being aspirated during this period from the right chest. Salyrgan was given at frequent intervals without restoring compensation. The patient was replaced in the oxygen chamber for three days and then operated on, remaining in the oxygen chamber for eight days after operation. He had a slight postoperative reaction.

The vital capacity was 800 to 900 before oxygen treatment, rose to a high of 1,350 before operation and was 1,150 after operation. Venous pressure before operation was 45, velocity of blood flow 45 seconds (Decholin). Salyrgan and thoracenteses continued to be necessary after operation and the patient showed no improvement. Four weeks after the operation, he died of bronchopneumonia.

In this patient with maximal cardiac failure, thyroidectomy appeared to be of no benefit. The progressive nature of the pathologic process was uninterrupted by the attempt made to lessen the work of the heart.

Case 10 Female, aged 65

Family History and Past History Irrelevant. *P I* Sixteen years ago, the patient began to suffer from attacks of pain in left arm, shoulder and precordium, at first induced by walking, later by changing from a warm to a cold room, and finally occurring at rest. During the week of admission, she had one severe attack with marked air-hunger and tachycardia.

Physical Examination The patient was a well-developed, well-nourished woman of 65, sitting quietly in bed, without dyspnea, cyanosis or orthopnea. Her heart was slightly enlarged, and the aortic arch on roentgen-ray appeared to be moderately dilated. No peripheral edema. Blood pressure 200/108 mm of Hg.

Laboratory Findings Electrocardiogram T_1 and T_2 inverted, T_3 upright, left preponderance. Basal metabolism minus 9 per cent. Vital capacity 2,200 c.c. Arterial oxygen saturation 95 per cent.

Course She was placed in the oxygen chamber for six days before operation and six days after. As indicated by chart 4, her pulse rate was substantially reduced during the period following admission to the oxygen chamber. She had a minimal postoperative reaction. There was an elevation of the pulse rate when oxygen was

discontinued Three days after leaving the chamber she was anxious to be out of bed She was discharged, free from pain, one week later She has been well since operation

In this patient, freedom from precordial pain was secured following thyroidectomy Despite her long history and her age, she withstood the operation extremely well She is in apparently good condition 13 months after the operation, except for the development of severe joint pains having the appearance of chronic arthritis

Case 11 Male, aged 59

Family History and Past History Irrelevant *P I* Nervousness and dyspnea began two and one-half years ago A diagnosis of hyperthyroidism was made but the patient refused operation Since that time, dyspnea has become worse, with increasing palpitation and ankle edema Two weeks prior to admission, following a sore throat, the patient became orthopneic and was confined to bed

Physical Examination Acutely ill man of 59 years, orthopneic and cyanotic, with massive edema of extremities Thyroid diffusely enlarged Lungs contained moist râles at both bases Heart greatly enlarged to left, sounds rapid, systolic murmur at apex Blood pressure 110/60 mm of Hg Liver felt 5 cm below costal margin

Laboratory Findings Hgb 92 per cent, rbc 5.3 millions, wbc 10,000, polynuclears 74 per cent Non-protein nitrogen 40 mg per cent Venous pressure 265 Electrocardiogram Auricular fibrillation, left preponderance

Course On rest in bed, nasal oxygen, morphine and digitalis he improved rapidly The basal metabolic rate was found to be plus 50 per cent On Lugol's solution for one week, the basal metabolic rate dropped to plus 17 per cent A partial thyroidectomy was performed under the same conditions as in the previous cases, with nasal oxygen and local anesthesia, the patient having been kept in the oxygen chamber for five days before and five days after operation He had very little postoperative reaction The basal metabolic rate 18 days after operation was plus 1 per cent He was discharged, ambulatory and improved Fibrillation with a slow ventricular rate was present

This was the only patient in the series in whom a partial thyroidectomy was done The symptoms of cardiac failure were precipitated by hyperthyroidism and it was felt that reduction to a normal oxygen consumption would be adequate to restore compensation The smooth postoperative course in this type of case, cardiac failure with hyperthyroidism, was not dissimilar to that seen in the cases of heart disease recited above

Case 12 Female, aged 30

Family History Grandmother had rheumatism *Past History* Pneumonia at four years, scarlet fever at six years, no rheumatic fever, chorea at six years *P I* At the age of 15, patient first noticed palpitation of the heart on exertion, accompanied by shortness of breath Four years ago increasing dyspnea took place, and one year later she entered the hospital because of cardiac insufficiency Patient improved but never became free from edema, dyspnea on slight exertion and a swollen abdomen A second admission became necessary on June 18, 1935, because of increasing orthopnea and swelling of the legs and abdomen

Physical Examination A thin, poorly developed negress, moderate orthopnea and dyspnea, doubtful cyanosis Lungs Dullness and diminished breath and voice sounds, with moist râles at both bases posteriorly Heart Greatly enlarged, dullness at base 8 cm, in the fourth interspace to the right 5 cm, 13.5 cm to the left in the fifth interspace, rhythm totally irregular, systolic and diastolic murmurs at the apex, a diastolic and rough systolic murmur at the aortic area, blood pressure 130/60 mm of Hg Abdomen tense and full with a fluid wave, liver palpable at the level of the umbilicus, spleen felt at the costal margin

Laboratory Findings Hgb 75 per cent, rbc 4.2 millions, wbc 8,700, polynuclears 75 per cent Non-protein nitrogen, 26 mg per cent, serum protein 5.9 per

cent Venous pressure 270 to 310 Electrocardiogram Auricular fibrillation, ventricular rate 50, left preponderance, T_1 upright, T_2 and T_3 inverted Basal metabolic rate plus 8 per cent

Course Patient was treated in the hospital with rest in bed, digitalis and salyrgan for four months, when thyroid ablation was decided upon At this time her vital capacity was 1,150 c c , pulmonary ventilation 62 liters per minute, arterial oxygen saturation 91 per cent, circulation time 40 seconds (by sodium cyanide method) Patient was placed in the oxygen chamber for two and one-half weeks prior to operation, which was done under oxygen and local anesthesia In this patient, the only one of the series, a postoperative reaction took place, the temperature rising to 103.6° F and pulse from 62 to 96 on the day following the operation, returning to normal on the third day postoperatively The patient was removed from the oxygen chamber six days after operation

Four weeks after operation the patient no longer experienced any heart consciousness However, she began to accumulate fluid in the abdomen again and required salyrgan The basal metabolic rate at that time was minus 21 per cent

This patient represents a case of cardiac insufficiency that was not compensated by rest in bed Although she had a febrile postoperative reaction, the behavior of her heart was at no time embarrassed The patient did not make any substantial improvement and died six months later of congestive failure

DISCUSSION OF RESULTS

In presenting 12 cases of thyroid ablation in patients suffering from heart disease, we wish to formulate no general conclusions concerning the value of the procedure nor of the special use of oxygen therapy in conjunction with it Our intention is rather to discuss the results of our experience as a guide to further work in the treatment of cardiac disorders

That no mortality occurred as a result of operation cannot in such a small series be ascribed to the use of oxygen or to the skill of the surgeon However, in some instances maximally severe cases of congestive heart failure were chosen, patients who had been bed-ridden five to 18 months, who were brought to an operable stage without manifestations of cardiac insufficiency by residences in a 50 per cent oxygen atmosphere The severity of congestive failure may be estimated by the marked reduction of the vital capacity in five of our patients who at some time before operation showed the following readings case 1, 900 c c , case 2, 1,100 c c , case 8, 750 c c , case 9, 800 c c , case 12, 1,100 c c In the series of Blumgart and his collaborators, the lowest vital capacity among 31 cases tested preoperatively was 1,350 c c * In their review of 18 months' experience with thyroid ablation, they report that in 60 cases of congestive failure six have died since operation and six died operative deaths, i e , within the first three days after operation Their operative mortality was then 10 per cent They state that all deaths occurred in patients in congestive failure at the time of operation Our own series is too small to make statistical comparison with theirs We wish merely to point out that our interest has centered chiefly in cases in whom compensation in room air under conditions of ambulatory activity could not be obtained, the severity of whose condition is in some instances revealed by the low level of their vital capacities (table 7) We

* Personal communication

TABLE VII
Summary of Clinical Data in 12 Patients with Cardiac Insufficiency on Whom Thyroid Ablation Was Performed

Case	Age	Sex	Diagnosis	Arterial Oxygen Saturation	Vital Capacity	Venous Pressure	Basal Metabolism	Con-gestive Failure	Cardiac Pain	Outcome
1	34	F	Rheumatic valvular heart disease, cardiac insufficiency, ascites	94	900-1100	130-153	-13	4+	0	Marked improvement
2	56	F	Rheumatic valvular heart disease, cardiac insufficiency, ascites	93	1100-1375	260	-3	4+	0	Marked improvement
3	22	F	Rheumatic valvular heart disease, cardiac insufficiency	95	1200-1800	28	-10	3+	0	Moderate improvement
4	51	M	Arteriosclerosis, coronary sclerosis	92	2400	68	-2	2+	3+	No improvement
5	51	M	Arteriosclerosis, coronary sclerosis, aortic stenosis	96	2950	10	+24	0	4+	No improvement, death four months postop
6	57	M	Arteriosclerosis, coronary sclerosis, hypertension	95	2000	12	+3	1+	3+	Moderate improvement
7	43	F	Arteriosclerotic heart disease, cardiac insufficiency	—	2000	135	+19	2+	0	Moderate improvement
8	46	F	Rheumatic valvular heart disease, cardiac insufficiency, ascites	—	750	278	+5	4+	0	Moderate improvement
9	61	M	Arteriosclerosis, coronary sclerosis, hypertension, emphysema, cardiac insufficiency	—	800-900	45	+12	4+	2+	No improvement, death one month postop
10	65	F	Arteriosclerotic heart disease, coronary sclerosis	95	2200	—	-9	0	4+	Moderate improvement
11	59	M	Hyperthyroid heart, cardiac insufficiency	—	—	265	+50 to +17	3+	0	Moderate improvement
12	30	F	Rheumatic valvular heart disease, cardiac insufficiency, ascites	91	1150	310	+8	4+	0	Minimal improvement, died 6 months later

wish to draw attention to the fact that preoperative oxygen treatment was employed to increase the efficiency of the circulation, that oxygen was used during and after the operation to prevent anoxemic shock, and finally that under these circumstances there was little or no postoperative reaction, as revealed by the clinical condition of the patients and the charts of their pulse, respiration and temperature. It seemed likely to us, as a result of an experience with an admittedly small number of patients, that the very severe case of congestive failure in whom an operative mortality of some degree might otherwise be expected could with the employment of this program of preoperative and postoperative treatment be more safely conducted through the procedure of thyroid ablation. Furthermore, our impulse to utilize thyroidectomy was in the main directed toward this type of case. In two instances, in which prolonged oxygen treatment did not achieve a satisfactory state of compensation, the majority opinion decided against thyroidectomy. In most of the cases, the favorable effect of oxygen treatment was apparent, especially by the lowering of the pulse rate before operation and its elevation when oxygen treatment was discontinued after the operation, examples of which occur in the charts presented. In addition, the scarcity of the symptoms of postoperative reaction impressed us.

The beneficial effect of oxygen therapy immediately following major surgical operations has been reported by Boothby and Haines,²² Binger, Judd, Moore and Wilder.²³ Judd²⁴ has already observed, "We feel there can be no question that the use of oxygen postoperatively has a definitely favorable effect on the prevention and treatment of pulmonary edema and congestion. In our opinion, we have materially reduced the incidence of postoperative pneumonia since using oxygen therapy freely following major surgical procedures."

In presenting this communication, we wish to record mainly the clinical data which we observed, the opinions we derived from them are tentative and must await a longer period of trial before we can accept them as established conclusions.

In viewing the results of thyroidectomy itself, we have been especially struck by the improvement in two maximally severe cases of congestive failure, numbers 1 and 2, both due to rheumatic heart disease. In these cases, the change from a bed-ridden existence to one of ambulatory activity was striking and could be distinctly ascribed to thyroid ablation. In neither of the patients was clinical myxedema a troublesome feature. In another case of severe congestive failure, number 8, the time interval has been too short to permit prediction of her ultimate improvement. She is subjectively considerably improved. The vital capacity has increased from 750 cc to 1,200 cc. The venous pressure has fallen from 250 to 97. Paracentesis of the abdomen has been reduced from once a week to once in two weeks. The result in case number 3, one of congestive failure of more

moderate degree than the three above mentioned, is not striking, but it can be safely said that some improvement in the function of her circulation has occurred and that subjectively she is better than prior to operation. The patient whose congestive failure was associated with hyperthyroidism, number 11, is much improved, as might be expected. He was included in the series because he was subjected to the same program of oxygen treatment in association with thyroidectomy. The case of congestive failure, number 9, in whom coronary arteriosclerosis was at the basis of his heart disease, was unimproved, and died one month after operation. His failure was progressive from the time of entrance to the hospital and was uninfluenced by thyroid ablation. The sixth case of congestive failure, number 7, was one of moderate severity. She has been subjectively improved and is able to carry on distinctly increased ambulatory activity since the operation, but the time interval that has elapsed is too small for more to be said than this. The seventh case of congestive failure, number 12, became free from heart consciousness but no substantial improvement took place and the patient died six months later of congestive failure.

There remain four cases in which operation was performed for cardiac pain in the absence of congestive failure. In two, cases 6 and 10, relief from pain was definite, the patients themselves were pleased with the results of the operation and the procedure could be said to have justified itself. The occurrence of severe facial myxedema in one, case 6, ultimately ameliorated by thyroid extract, for a time clouded the patient's satisfaction with the relief of his heart pain. In the remaining two cases, an unsuccessful result was obtained. In one of them, case 4, the patient had a psychoneurosis sufficiently severe as to obscure any benefit he might have received. He did not appear to be subjectively or objectively improved. In the other, case 5, a temporary period of improvement was followed by a progressively severe course ending in death. It should be mentioned in his case that the basal metabolism did not go below minus 20 per cent, and that at autopsy a nodule of hyperplastic thyroid tissue was found. In addition to arteriosclerosis he had a marked aortic stenosis. The other three cases of cardiac pain were presumably cases of coronary arteriosclerosis.

The laboratory data submitted in the tables do not require detailed comment. The blood cholesterol was elevated after thyroidectomy, which is in accord with the careful studies on this point by the original authors²⁵. The oxygen saturation of the arterial blood in the cases studied was either slightly lowered or normal. The venous pressure and vital capacity measurements indicate the severity of congestive failure in the individual cases. The blood volume in two cases was reduced after thyroidectomy, suggesting lessened work for the heart. The vital capacity was moderately increased in some cases, although this was not a marked or consistent outcome. The red blood cells tended to show a decrease of a half million to a million cells, with pro-

portionate decrease in hemoglobin, as previously mentioned by Blumgart and his collaborators. The venous pressure was definitely decreased in some patients, uninfluenced in others.

COMMENT

We are unable to formulate any firm indications for thyroid ablation in the treatment of heart disease, our own experience is too limited and the total lapse of time since the procedure was inaugurated is too brief to permit of final judgment. Nevertheless, we did select the cases that make up the present report with certain principles in mind.

The patient with congestive failure who was bed-ridden all the time, or most of the time, became a potential candidate for thyroidectomy. Also, when the periods of compensation in a patient were very brief, such as a matter of a few months, we regarded these recurring attacks of cardiac insufficiency as indicating a very small cardiac reserve. In other words, the procedure seemed justified when little expectation of comfort could be expected without it.

In the cases with cardiac pain, the existence of unrelieved, severe, frequent pain over the heart raised the question of thyroidectomy. In both groups of cases, the presence of a stationary lesion, rheumatic or arteriosclerotic, increased the indication for operation. Cases that appeared to regain a somewhat stable compensation on oxygen therapy alone were not subjected to thyroidectomy.

We accepted certain contraindications such as a basal metabolism under minus 15 per cent, the presence of nephritis, advanced age—over 75 years—or too youthful an age, such as before puberty. Also, we have avoided choosing patients with syphilitic heart disease, since the pathological process in these cases might be expected to advance despite the production of a lowered oxygen consumption. In addition, we believe the patient should be brought into a state of relative cardiac sufficiency before operation. Oxygen therapy was specially used for this purpose. It was not demanded that these patients should be able to be compensated in room air. Our belief was that if they could be brought to a state of relative cardiac sufficiency in an oxygen chamber, the operation could then be performed with the patients compensated, even if the inhalation of oxygen-enriched atmospheres was necessary for the maintenance of compensation, the fact that the operation was done while oxygen inhalation was still being continued removed the danger of anoxemic shock. It is true that a sudden removal from a high oxygen environment to that of atmospheric air may precipitate cardiac collapse in severely ill patients. However, the method here pursued was to avoid any interruption of oxygen therapy until a safe period following the operation appeared. The subsequent reduction in cardiac work then

allowed the patient to pursue an ambulatory existence without the help of oxygen therapy, as was illustrated by the two severe rheumatic cases of congestive failure in our series

In the case of angina pectoris, we would now feel doubtful about selecting patients who had such severe coronary artery disease as to suggest an advancing process. The clinical course of these patients is difficult to predict, but in so far as it is possible to do so, the patient with very troublesome pain but with little evidence of progressive coronary disease, would appear a more justifiable candidate than one with very marked and probably advancing coronary changes. In this group, the danger of cardiac failure attending the operation is less real than in the congestive failure patient who is unable to be compensated out of a bed, although postoperative deaths have been reported in this group (Cutler²⁶). We adopted a practice of employing oxygen in these cases also, using a smaller preliminary period of treatment. Doubtless, many of these patients would have gone through the operation without reaction. However, anginal pain is itself a result of anoxemia of the heart muscle, and in many cases can be relieved by inhalation of oxygen.¹² In two of our cases, anginal pain and increased pulse rate recurred four days after the operation when the oxygen concentration of the chamber was lowered and disappeared with elevation of the oxygen concentration. The presence of anemia increases the indication for oxygen treatment in this group.* During a period of stress which an operation induces, the inhalation of oxygen would tend to counteract the development of oxygen debt and therefore tend to maintain the efficiency of the circulation. In patients with anginal pain without congestive failure, the use of oxygen treatment according to the program outlined would therefore appear to be helpful, although not as valuable a procedure as in the patient whose cardiac insufficiency is an immediate problem.

SUMMARY

In 12 patients a program of preoperative, operative and postoperative oxygen treatment has been employed as an adjuvant to ablation of the thyroid gland in cases of heart disease. In patients with congestive failure, their circulation efficiency was improved by the preoperative period of residence in an oxygen chamber. During the operation itself and for a time following it, oxygen therapy tended to prevent the development of oxygen debt and anoxic shock. Charts showing the effect of oxygen treatment and the absence of severe postoperative reactions have been drawn up. There were no operative deaths.

* Pickering and Wayne²⁷ reported observations on a series of 25 patients with anemia eight of whom complained of pain over the sternum induced only by exercise and relieved by rest, in six this pain was no longer experienced after the anemia had been cured, while in two it persisted. The authors concluded from their experiments that the essential factor in the production of anginal pain in anemic patients is a diminished supply of oxygen to the working cardiac muscle and not an inadequate flow of blood.

The physiological effects of oxygen therapy in cardiac decompensation have been reviewed. Its helpfulness in this condition has added further evidence in support of our belief in the value of this form of therapy.

The results of thyroidectomy have been commented upon individually in this study without attempting to formulate firm conclusions. Our interest has been aroused chiefly in severe cases of congestive heart failure of rheumatic etiology in the absence of an active rheumatic process. In two cases of this type followed for a period of over two years, the gain of cardiac efficiency has been striking. The treatment of angina pectoris by thyroidectomy seems to us more wisely restricted to those patients who have troublesome anginal pain in the absence of clinical and electrocardiographic evidence of an advancing sclerosis of the coronary artery. In two cases of this type the clinical betterment which ensued completely justified the operation. Three patients, two with cardiac pain and one with congestive failure and cardiac pain, were not helped. One case of congestive heart failure was not improved and died six months later. The remaining four were improved, the time elapsing since operation being insufficient to permit giving a reliable estimate of the degree of benefit.

BIBLIOGRAPHY

- 1 (a) BARACH, A L, RICHARDS, D W, MILHORAT, A T, and LEVY, R L Effects of oxygen therapy on patients with congestive heart failure, *Proc Soc Exper Biol and Med*, 1929, **xxvii**, 308
- (b) BARACH, A L, and RICHARDS, D W Effects of treatment with oxygen in cardiac failure, *Arch Int Med*, 1931, **xlvi**, 325
- (c) LEVY, R L, and BARACH, A L Therapeutic use of oxygen in coronary thrombosis, *Jr Am Med Assoc*, 1930, **xvii**, 1363
- (d) BARACH, A L Therapeutic use of oxygen in heart disease, *ANN INT MED*, 1931, **v**, 428
- (e) BARACH, A L, and LEVY, R L Oxygen in the treatment of acute coronary occlusion, *Jr Am Med Assoc*, 1934, **cii**, 1690
- (f) BARACH, A L The treatment of asphyxia in clinical disease, with especial reference to recent developments in the use of oxygen in heart disease, *N Y State Jr Med*, 1934, **xxxiv** (No 15)
- (g) RICHARDS, D W, and BARACH, A L Prolonged residence in high oxygen atmospheres Effects on normal individuals and on patients with chronic cardiac and pulmonary insufficiency, *Quart Jr Med*, 1934, **xi**, 437
- (h) BARACH, A L Treatment of heart failure by continuous oxygen therapy, *Anesth and Analges*, March-April, 1935
- 2 (a) BLUMGART, H L, LEVINE, S A, and BERLIN, D D Congestive heart failure and angina pectoris The therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity, *Arch Int Med*, 1933, **li**, 866
- (b) FRIEDMAN, H F, and BLUMGART, H L Treatment of chronic heart disease by lowering the metabolic rate The necessity for total ablation of the thyroid, *Jr Am Med Assoc*, 1934, **cii**, 17
- 3 (a) BLUMGART, H L, and WEISS, S Studies on the velocity of blood flow II The velocity of blood flow in normal resting individuals and a critique of the method used, *Jr Clin Invest*, 1927, **iv**, 15 VII The pulmonary circulation time in normal resting individuals, *Ibid*, 1927, **iv**, 399

- (b) BLUMGART, H L, GARGILL, S L, and GILLIGAN, D R Studies on the velocity of blood flow XIII The circulatory response to thyrotoxicosis, Jr Clin Invest, 1930, ix, 69 XIV The circulation in myxedema with a comparison of the velocity of blood flow in myxedema and thyrotoxicosis, Ibid, 1930, ix, 91 XV The velocity of blood flow and other aspects of the circulation in patients with "primary" and secondary anemia and in two patients with polycythemia vera, Ibid, 1931, ix, 679
- (c) BLUMGART, H L The velocity of blood flow in health and disease The velocity of blood flow in man and its relation to other measurements of the circulation, Medicine, 1931, x, 1
- 4 BLUMGART, H L, BERLIN, D D, RISEMAN, J E F, and WEINSTEIN, H H Total ablation of the thyroid in angina pectoris and congestive failure, Jr Am Med Assoc, 1935, civ, 17
 - 5 BLUMGART, H L Personal Communication
 - 6 CAMPBELL, J A Further observations on oxygen acclimatization, Jr Physiol, 1927, lxiii, 325 Comparison of pathological effects of prolonged exposure to carbon monoxide with those produced by very low oxygen pressure, Brit Jr Exper Path, 1929, x, 304 Hypertrophy of heart in acclimatization to chronic carbon monoxide poisoning, Jr Physiol, 1932, lxxvii, 8
 - 7 KATZ, L N, KERRIDGE, P T, and LONG, C N H Lactic acid in mammalian cardiac muscle III Changes in hydrogen-ion concentration, Proc Roy Soc, Series B, 1925-26, xcix, 26
 - KATZ, L N, and LONG, C N H Lactic acid in mammalian cardiac muscle I The stimulation maximum, Proc Roy Soc, Series B, 1925-26, xcix, 8
 - 8 EVANS, G T Quoted from Meakins, J C⁹
 - 9 MEAKINS, J C Modern muscle physiology and circulatory failure, ANN INT MED, 1932, vi, 506
 - 10 BEDDARD, A P, and PEMBREY, M S Observations on pulmonary ventilation in disease, Brit Med Jr, 1908, ii, 580
 - 11 CAMPBELL, J M H, HUNT, G H, and POULTON, E P Examination of blood gases and respiration in disease with reference to cause of breathlessness and cyanosis, Jr Path and Bact, 1923, xxvi, 234
 - 12 MEANS, J H, and NEWBURGH, L H Studies of the blood flow by the method of Krogh and Lundhard, Trans Assoc Am Phys, 1915, xxx, 51
 - 13 HARROP, G A The oxygen and carbon dioxide contents of arterial and venous blood in normal individuals and in patients with anemia and heart disease, Jr Exper Med, 1919, xxx, 241
 - 14 BARACH, A L, and WOODWELL, M N Studies in oxygen therapy with determinations of blood gases I In cardiac insufficiency and related conditions, Arch Int Med, 1921, xxviii, 367
 - 15 CAMPBELL, J M H, and POULTON, E P Effect on breathless subjects of residence in oxygen chamber, Quart Jr Med, 1927, xx, 141
 - 16 PEABODY, F W, and co-workers Summarized in Harvey Lectures, 1916-1917, Series of papers in Arch Int Med, 1915-1922 Also, Studies on acidosis and dyspnea in renal and cardiac disease, Arch Int Med, 1924, xiv, 236
 - 17 VON BASCH, S Klinische und experimentelle Studien, Bd 1-3, 1891-1896, A Hirschwald, Berlin
 - 18 HARRISON, T R Failure of the circulation, 1935, Williams and Wilkins Co, Baltimore, pages 128, 172, 173
 - 19 UHLFABRUCK, P Das Cheyne-Stokesche Atmen, Ztschr f d ges exp Med, 1928, lix, 656, ibid, 1930, lxxiv, 1
 - 20 JANSEN, K, KNIPPING, H W, and STROMGFRGER, K Beitr z Klin d Tuberk, 1932, lxxx, 304

- 21 BARACH, A L New type of oxygen chamber, Jr Clin Invest, 1926, ii, 465
- 22 BOOTHBY, W M, and HAINES, S F Oxygen therapy, Jr Am Med Assoc, 1928, xc, 372
- HAINES, S R, and BOOTHBY, W M Values of oxygen treatment after thyroidectomy, Am Jr Surg, 1929, vi, 1
- 23 BINGER, M W, JUDD, E S, MOORE, A B, and WILDER, R M Oxygen in the treatment of patients with postoperative pneumonia, Arch Surg, 1928, xvi, 1047
- 24 JUDD, E S Quoted from BOOTHBY, W M Oxygen therapy, Jr Am Med Assoc, 1932, xcix, 2026
- 25 GILIGAN, D R, VOLK, M C, DAVIS, D, and BLUMGART, H L Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris VII Relationship between serum cholesterol values, basal metabolic rate and clinical aspects of hypothyroidism, Arch Int Med, 1934, liv, 746
- 26 CUTLER, E C Total thyroidectomy for heart disease, Minnesota Med, 1935, xviii, 421
- 27 PICKERING, G W, and WAYNE, E J Observations on angina pectoris and intermittent claudication in anemia, Clin Sci, 1934, i, 305

THE THERAPEUTIC ACTION OF THE NUCLEOTIDES, THE TREATMENT OF THE WHOLE BLOOD PIC- TURE WITH FERROUS ADENYLATE*

By SIMON L. RUSKIN, M D , and ELIHU KATZ, M D , *New York, N Y*

SINCE Rothmann, in 1931, showed that the hemoglobin percentage and the red cell count in a series of patients suffering from widely different diseases bore a fairly constant relationship to the amount of adenylic nucleotide in the blood, there has been a progressively increasing interest in the physiologic rôle of adenylic acid. The *Annual Review of Biochemistry* lists 114 separate papers in one bibliography. In the light of recent investigation, this study has become all the more interesting because of the general enthusiasm which first greeted nucleic acid therapy twenty years ago, and its subsequent failure to materialize. The explanation for this, apparently, lies in the fact that nucleic acid is composed of two groups of nucleotides representing physiologic antagonists in equal amounts and is thus relatively inactive. The prediction of our former teacher, Prof. John Mandel, that the unlocking of nucleic acid would usher in a new era of physiologic chemistry, appears to be approaching realization.

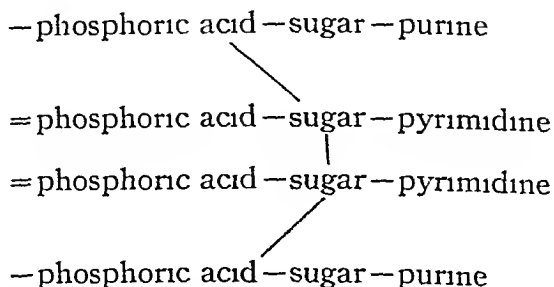
It is well for us to consider, briefly, the formation of nucleic acid before studying the characteristics of the nucleotides which form it.

Nucleic acid when conjugated with albumin or globulin forms a nucleoprotein. As a rule the protein elements may change with the different tissues where the nucleoprotein is formed but the nucleic acid radicals are relatively constant.

Nucleic acid is composed of four nucleotides, two of which are purines, having as the nitrogen containing base adenine and guanine respectively. The other two nucleotides are pyrimidines having the nitrogen containing bases thymine and cytosine. In plant nucleic acid instead of thymine we have uracil.

All four nucleotides have a common structure, thus, the base is united with a glucoside which, in animal nucleic acid is D-ribose, as well as to phosphoric acid.

Thus a picture of nucleic acid, according to Dr. P. A. Levene, is as follows:



* Read in part at the American Chemical Society Meeting at St. Petersburg, Florida, 1933. Received for publication November 27, 1935.

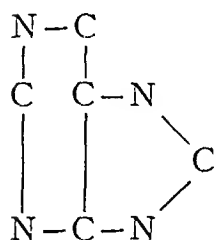
If we group the nucleotides in respect to their physiologic action, we get a schematic arrangement as follows

ANALYSIS OF NUCLEOTIDE ACTION

NUCLEIC ACID

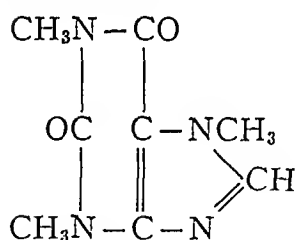
Adenine Nucleotide

Guanine Nucleotide



Purine structure resembling
caffeine, etc

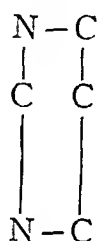
Stimulative



- 1 Stimulates reticulo-endothelial system, and induces leukocytosis
- 2 Increases coronary circulation
- 3 Participates in carbohydrate metabolism
- 4 Participates in muscle metabolism
- 5 Acts as a coenzyme
- 6 Is a glandular stimulant

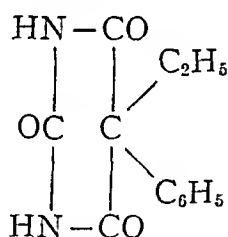
Cytidilic Nucleotide

Uridylic Nucleotide



Pyrimidine structure
resembling phenobarbital

Depressive



- 1 Precipitates toxins and binds toxalbumin
- 2 Induces leukopenia on injection
- 3 Inhibits bacterial growth
- 4 Is antiseptic in stronger dilutions
- 5 Acts like barbiturates on metabolism

It can therefore be readily seen that, in dealing with the individual nucleotides, we are working with substances radically different from the larger molecule, the nucleic acid. The situation may be considered as analogous to the relationship which coal tar bears to its various physiologically active fractions. This fractionation of nucleic acid has made available a new series of physiologic agents. The isolation of the nucleotides is both costly and difficult, but the value of separating these constituents of nucleic

acid was well pointed out by Doan who states that, "The definite and usually considerable leukocytosis that followed the intravenous injections of relatively large doses (1 gm of sodium nucleinate), in their series of normal rabbits, was proved to be of unquestionable bone marrow origin. However, a preliminary leukopenia occurred, sometimes lasting for a number of hours before the peripheral leukocytosis was observed, an obviously undesirable phase in the reaction

It was then determined to see whether this 'active principle,' affecting the myeloid foci in bone marrow, might not be contained in some of the degradation products of nucleic acid, as distinct from the accompanying leukopenia producing factor of the larger molecule. Chemically pure crystalline adenylic and guanylic acid were later tested. These products all gave an immediate neutrophilic response without preliminary leukopenia which recommended them as preferable to the larger nucleinate molecule for clinical use."

Of the four nucleotides, the adenine nucleotide, adenylic acid, has received the greatest amount of attention. Rothmann has shown that there is a direct correlation between the adenine nucleotides and the erythrocyte count and the hemoglobin percentage. This correlation holds in the various conditions ranging from severe anemia to polycythemia. The influence of adenylic acid on the circulation is further shown by the work of De Caro who demonstrated that adenylic acid isolated from yeast nucleic acid (1) lowers the blood pressure, (2) abolishes motility of the intestine, and (3) produces bradycardia. These effects are independent of the sympathetic and para-sympathetic innervation since they are observed in the same degree after the administration of atropine or ergotamine. Similar observations were made by Bennet and Drury whose investigations revealed that adenylic acid is a constituent of many tissues, being found in great amount in striated and heart muscle. It is apparently liberated from injured tissues and may be a contributing factor in inflammations and traumatic shock. The biologic effects of adenylic acid have been found to be identical with those of adenosine, in that (1) the blood pressure is lowered, (2) the vessels of the perfused rabbit lung are constricted, (3) the isolated virgin guinea pig uterus is caused to contract and (4) in that a general leukocytosis may be produced. Drury, furthermore, found that in the perfused rabbit heart, the addition of either guanylic or adenylic acid leads to a brief primary decrease followed by a prolonged increase in the amplitude of the mechanogram. He did not find adenine or guanine to have such influence and concluded, therefore, that the nucleic acid derivatives which contain a phosphoric acid grouping were capable of producing the change.

This is, however, somewhat at variance with the observations of Drury and Weeds on the influence of adenosine in dilating the coronary arteries of the heart. They showed that yeast or muscle adenylic acid have about 66 per cent of the effect of adenosine, whereas inosinic acid, adenine, guanosine,

and sodium nitrate were about 33 per cent as effective as adenosine. Thymus and yeast nucleic acid have an inconstant effect. A slight constriction is occasionally produced. These conclusions are further corroborated by Weld, who found that adenosine caused marked dilation of the coronary vessels, being twenty times as powerful as sodium nitrate. Adenylic acid (yeast or muscle), adenine, or guanosine also dilated the coronary vessels but were not as effective as adenosine.

Among the earlier investigations of the nucleotides, adenylic and guanylic acid, is that of Rosenfeld who found, upon the injection of these acids in the form of the sodium salts, an increase in the uric acid and total nitrogen of the urine. This increase in total nitrogen was greater than the nitrogen contained in the injected substances, while the increase in uric acid was only 10 per cent of the value calculated for the complete conversion of the purine. It is not unlikely, therefore, that the effect on the composition of the urine is explained, in part at least, as due to an increased metabolism and increased glandular activity.

The occurrence of adenylic acid and its isolation from the blood were demonstrated by Hoffman, Jackson, Buell and Perkins. Its presence in and isolation from milk has been proved by Kay, from brain by Pohle, from muscle by Ostern and from kidney by Embden.

How significant a rôle adenylic acid plays in the normal metabolism is gleaned from its relationship to carbohydrate metabolism. The investigations of Myrbock and Euler have shown that cozymase activity is associated with a nucleotide which, in certain respects, resembles muscle adenylic acid. It has not been obtained in crystalline form, nor has a crystalline salt been prepared from it. Studies of the rate of hydrolysis show that this nucleotide belongs to the same group as inosic acid and muscle adenylic acid, but it is clearly distinguished from the adenosine phosphoric acid obtained from yeast nucleic acid.

That adenylic acid plays an important rôle in metabolism is further substantiated by the observations of Lehmann who showed that the esterification with trihydrogen phosphate through the lactic acid enzyme system proceeds only in the presence of adenylyl-pyrophosphate plus magnesium. He showed that frog muscle extract loses its ability to hydrolyze glycogen after standing at 20° for two to three hours. Adenylyl-pyrophosphate isolated from a fresh muscle can completely restore this lactic acid forming ability to the inoculated extract. Myerhof, Lohmann and Meyer have also demonstrated that the lactic acid forming system of muscle or muscle extracts consists of the thermolabile enzyme and the thermostable coenzyme. The coenzyme must consist of an autolysable and non-autolysable fraction. The former is the adenylyl-pyrophosphate. The complement of the coenzyme present in autolyzed boiled juice is the magnesium. Therefore, the magnesium salt must be added besides the adenylyl-pyrophosphate to completely

restore its lactic acid forming ability From these considerations it is concluded that the system,

- (1) inorganic phosphate,
- (2) adenylypyrophosphate,
- (3) and the magnesium,

constitutes the coenzyme of lactic acid formation

Jacobson has in addition shown that an enzyme liberating trihydrogen phosphate from adenylypyrophosphate is present abundantly in the liver and to lesser extent in the kidney Evidence is presented for considering this enzyme as distinct from other phosphatases

Euler and Myrbock define cozymase as that substance which brings about the typical carbohydrate cleavage in an otherwise inactive mixture of sugar, phosphate, zymphosphate, apozymase, and magnesium salts They found that the purest preparations of this consisted almost entirely of a substance closely related to adenylic acid (muscle) The close relationship of cozymase to adenylic acid was also demonstrated in an interesting manner by Svengard who showed that injections of cozymase into the jugular vein of rabbits under Wrettan narcosis caused a lowering of blood pressure This effect was independent of the specific action of the cozymase, since inactivation of the coenzyme by heating did not interfere with the lowering of the blood pressure Pure adenylic acid of yeast is somewhat more active in this respect, possibly because of the fact that the cozymase is not an entirely pure adenylic acid The introduction of the thio-methyl group into the adenosine molecule apparently does not diminish this special action The action of cozymase in lowering the blood pressure is a non-specific effect of the adenylic acid or the homologous adenosine derivatives This is further corroborated by Zipf in his observations with muscle adenylic acid

Not only do we find adenylic acid playing an important rôle in carbohydrate metabolism, but it is no less significant in its influence on muscle metabolism Thus, Schmidt showed that it undergoes enzymic deamination when treated with the pulp or press juice from rabbit muscle The free purine on the other hand remains practically unaltered when subjected to this treatment Likewise, Embden and Wassermeyer performed experiments which proved that the source of the ammonia in muscle contraction is from the NH_2 group in adenosine phosphoric acid The influence of adenylic acid during muscle contraction has been carefully studied by Embden and Lehnartz who found the amounts of free pentose and pentoside in muscle increased following contraction, which indicated that the increased phosphate regularly observed was liberated from an adenylic acid complex Many authors further suggest that in the recovery period of muscle contraction the pyrophosphoric acid is resynthesized both from the free trihydrogen phosphate and the split off product of adenylic acid For confirmation, they point to the increase of free pentose during the two hour recovery period of fatigued muscle

These studies of the purine nucleotides thus reveal the beginning of an analytic break-up of nucleic acid into a series of substances possessing independent properties in balanced systems not yet completely revealed. From the physiologic standpoint the separation of the purine from the pyrimidine nucleotides makes a radical difference in availability, for, the purine nucleotides possess valuable stimulative action on the reticulo-endothelial system and form a valuable vehicle for metal salt therapy while the pyrimidines, because of their depressing action on the reticulo-endothelial system, are undesirable for injection. On the other hand, the increased solubility of the pyrimidines makes them available for salts such as the silver salts, that are used in topical application. The interesting disclosure of Williams, that vitamin B is a pyrimidine thiazole compound, lends added interest to these substances.

One of us, Dr. Simon L. Ruskin, has therefore synthesized all the metal and metalloids salts of adenylic and guanylic acid as well as the metal and metalloids salts of cytidilic and uridylic acids.

In studying these preparations, it is interesting to note that ferrous adenyate provides a non-toxic iron for intramuscular or intravenous use that is stable, readily soluble, and non-irritating on injection, having a pH close to neutral. How valuable the combination of iron with a physiologically occurring radical may be can be seen from Rothmann's study showing that the average value of this nucleotide in blood is from 15 to 18 mg per cent. He finds that there is a distinct correlation between adenylic acid and the erythrocyte count. In anemia the lowest values are found, in polycythemia the highest. The daily destruction of erythrocytes explains the relatively large amount of adenylic acid excreted in the bile. The injection of this nucleotide leads to a rise in excretion of uric acid in the urine. Rothmann believes that adenylic acid plays an important rôle in the endogenous metabolism of uric acid. Engelhardt regards the adenylyl pyro-nucleotide as a component of the coenzyme system of respiration. Thus, in employing ferrous adenyate we have a therapeutic agent in a more potent form not only for stimulating erythrocyte and leukocyte formation, but also for enhancing the respiratory coenzyme system in which the iron also plays a rôle.

In approaching the clinical study of the therapeutic action of the nucleotides, we selected, for this investigation, the influence of the nucleotides on the blood picture, leaving for later study the other aspects discussed in this paper. The relationship between hemoglobin, erythrocyte count and leukopenia has hitherto received but little study. Even though the proverbial tonic has always been directed toward hemoglobin and red cell formation, nevertheless, it appears that the white cell should really be the objective. Roberts and Kracke, in a comprehensive study analyzing the accumulated data in terms of white cell level and symptomatology, reviewed 8000 cases of private clinic patients. One of every four was found to have had a mild granulopenia. One of each two women patients, between the ages of 40 and 60, was neutropenic, and complaints of weakness, exhaustion and

fatigue, with a tendency to sleep, were twice as frequent in the granulopenic individuals as in those showing a normal white cell count. Eighteen per cent of the granulopenic group gave a chief complaint of nervousness. Furthermore, the severity of the symptoms paralleled, to a remarkable extent, the degree of granulopenia found.

In our own cases, cited below, the feeling of well being was far in excess of the rise in hemoglobin and erythrocytes, even though the latter increase was in itself considerable.

The relationship between leukopenia and anemia was further emphasized by Roberts and Kracke who say that, in the attack of pernicious anemia the granulocytes often decrease with the normocytes, and the characteristic granulocytes of pernicious anemia seem to be the first blood evidence of the attack and the last after remission has begun. If one could explain agranulosis, he might also be able to explain pernicious anemia.

The first extensive series of clinical tests was conducted with ferrous adenyate, prepared in half and one grain doses with the assistance of the Merck Research Laboratory. The clinical aspects were carefully followed by one of us, Dr. Elihu Katz, in selected cases. Although over 1,000 injections were administered in a wide variety of patients, no untoward local or general reaction was observed at any time. The case reports present several of those controlled by Dr. Katz (table 1).

Since the ferrous adenyate is the salt which has been selected for clinical trial, it is well to point out several of the factors relative to iron therapy. Since ferrous adenyate is soluble without the addition of ammonium, it is non-irritating and available for intravenous as well as intramuscular use. The Heath, Strauss and Castle report, that the parenteral administration of iron resulted in 100 per cent iron utilization, has established the value of parenteral iron medication and made possible a precise determination of iron need and supply. According to Fullerton, blood iron corresponding to 100 per cent hemoglobin (Haldane scale) is equal to 48 mg. per 100 c.c. Assuming blood volume to be 5 liters, a rise of 1 per cent hemoglobin is equivalent to a gain of $48/100 \times 50$ equals 24 mg. Fe as hemoglobin. Since a 1 per cent rise of hemoglobin may be considered as a satisfactory result from iron salt therapy, 24 mg. can be considered the essential therapeutic dose. This amount of iron is found in $1\frac{1}{2}$ grams of ferrous adenyate. When one compares this with the oral administration of 90 grains to supply the utilized amount of less than half a gram, one gets a better perspective of the relative merits of oral and parenteral therapy. The discomfort of daily use of large amounts of ferric ammonium citrate may be obviated by the parenteral route.

The immediate hormonal action of the adenyate radical on the circulation was apparent in all of the cases observed. During several hours following the injection, the patients would, as a rule, experience a sensation of exhilaration and a mild flushing of the skin. Several children showed a marked improvement in facial color. One of the patients showed an initial

TABLE I

Case	Age	Sex	Diagnosis	Injections				Comment
				1st, 2nd 3rd	4th 5th 6th	7th 8th, 9th	10th 11th, 12th	
No 1 A C	32	F	Secondary anemia, pyelitis	Hgb 58% R B C 3 240 000 W B C 5 300	70% 3,150 000 7 600	73% 3 720 000 7 800	77% 4 000 000 7 800	After 12 injections of ferrous adenyate and diet the patient showed marked improvement in the general physical condition. Repeated urinalysis still showed how ever faint traces of albumin and pus cells
				Hgb 61% R B C 2 980 000 W B C 5 900	70% 3 250 000 7,600	74% 3 340 000 7 500	80% 4 000 000 7 800	
				Hgb 63% R B C 3 200 000 W B C 7 400	71% 3 250 000 7 600	76% 3 600 000 7 500	81% 4 100 000 7 900	
No 2 R S	55	F	Chronic mitral diseases and secondary anemia	Hgb 62% R B C 3 140 000 W B C 4 500	65% 3 500 000 5 000	72% 3 900 000 6 300		There was rapid improvement and the patient frequently remarked that she never felt so well in years
				Hgb 62% R B C 3 200 000 W B C 4 500	65% 3 500 000 5 000	75% 4 200 000 8 016		
				Hgb 63% R B C 3 300 000 W B C 5 000	70% 4 000 000 6 200	78% 4 500 000 7 200		
No 3 C T	32	F	Psychoneurotic	Hgb 68% R B C 4 730 000 W B C 7 375	70% 4 550 000 7 200	74% 4 900 000 7 600	80% 4 900 000 8 000	Patient improved both mentally and physically
				Hgb 68% R B C 4 700 000 W B C 7 500	72% 4 400 000 7,000	76% 4 800 000 8 000	81% 5 000 000 8 300	
				Hgb 68% R B C 4 700 000 W B C 7 000	74% 4 800 000 7 500	78% 5 000 000 8 900	83% 5 000 000 8 500	
No 4 S H	31	F	Lacerations of the cervix and vagina secondary anemia possible cholecystitis	Hgb 75% R B C 3 910 000 W B C 4 088	75% 3 880 000 5 000	79% 3 880 000 6 200	85% 3 990 000 4 975	No definite diagnosis could be made. Patient improved steadily. Appetite returned. The blood pressure rose from 92 systolic to 110. She was loathe at first to admit improvement but after 12 injections frankly admitted she was better
				Hgb 70% R B C 3 600 000 W B C 4 000	78% 4 000 000 5 600	79% 3 900 000 5 000	85% 4 000 000 6 000	
				Hgb 73% R B C 3 640 000 W B C 4 200	77% 3 950 000 5 800	83% 4 000 000 5 800	85% 4 100 000 5 800	
No 5 F W	30	F	Psychoneurotic with secondary anemia	Hgb 79% R B C 4,200 000 W B C 5 700	81% 4 200 000 5 500	81% 4 300 000 6 000	85% 4 500 000 6,700	Patient responded nicely but not as rapidly. Still suffers from insomnia
				Hgb 79% R B C 4 250 000 W B C 5 500	80% 4 300 000 5 460	83% 4 500 000 6 000	86% 4 400 000 6 800	
				Hgb 82% R B C 4 300 000 W B C 5 600	80% 4,200 000 5 500	85% 4 300 000 5 940	89% 4 500 000 6 866	
No 6 C F	55	M	Hemorrhoids secondary anemia	Hgb 68% R B C 3 300 000 W B C 6 000	69% 3 200 000 6 600	77% 3 800 000 6 600	82% 3 900 000 7 200	While receiving the injections was treated locally for hemorrhoids by a rectal specialist. The local condition responded rapidly. Patient felt well
				Hgb 65% R B C 3 000 000 W B C 5,800	73% 3 500 000 6,500	78% 4 000 000 7 200	83% 3 900 000 7,100	
				Hgb 68% R B C 3 000 000 W B C 6 000	75% 3 600 000 6 500	81% 3 800 000 7 000	85% 4 200 000 7 200	

TABLE I—Continued

Case	Age	Sex	Diagnosis	Injections					Comment	
				1st	2nd	3rd	4th 5th 6th	7th 8th 9th		10th 11th 12th
No 7 H B	56	M	Duodenal ulcer	Hgb 68% R B C 3 200 000 W B C 6 800			68% 3 200 000 7 000	74% 3 680 000 7 800	82% 4 200 000 7 600	The occult blood in the stool disappeared. Patient improved. He was on a modified Sippy regime in addition to the ferrous adenylate
				Hgb 66% R B C 3 000 000 W B C 6 400			70% 3 600 000 7 600	81% 4 000 000 6 900	87% 4 300 000 7,800	
				Hgb 68% R B C 3 200 000 W B C 6 800			74% 3 800 000 7 400	80% 4 000 000 7 100	85% 4 200 000 8 600	
No 8 E L	44	F	Chronic cho- lecystitis secondary anemia lacer- ated cervix	Hgb 75% R B C 4 200 000 W B C 5 800			79% 4 300 000 6 200	84% 4 500 000 7 200	87% 4 500 000 7 000	Patient's physical condition improved to such an extent that operative interference was advised
				Hgb 74% R B C 4 190 000 W B C 5 700			81% 4 440 000 6 280	84% 4 500 000 6 800	88% 4 500 000 6 950	
				Hgb 76% R B C 4 280 000 W B C 5 900			80% 4 400 000 6 500	86% 4 530 000 7 100	87% 4 500 000 7 300	
No 9 K R	48	F	Gallstones	Hgb 79% R B C 3 800 000 W B C 7 300				83% 4 200 000 7 800		Patient was operated upon after the 11th injection because of acute gall-bladder colic. It is interesting to note that she made a speedy convalescence more so than is usually the case after an acute operation
				Hgb R B C W B C			81% 3 800 000 7 600		88% 4 500 000 8 300	
				Hgb 78% R B C 3 600 000 W B C 7 400				87% 4 250 000 7 900		
No 10 C M	42	F	Fibrotic uterus	Hgb 60% R B C 3 300 000 W B C 6 016			53% 2 800 000 6 100	68% 3 500 000 7 200	70% 3 600 000 7 200	Patient at first refused operation. After 12th injection felt better and decided to enter hospital. Hysterectomy was performed and patient made rapid and uneventful recovery. On discharge from hospital hemo- globin rose to 82 per cent r b c 4 500 000 w b c 7 400
				Hgb 62% R B C 3 000 000 W B C 6 300			64% 3 000 000 6 000	70% 3 600 000 6 600	72% 3 650 000 7 000	
				Hgb 60% R B C 3 000 000 W B C 6 500			66% 3 200 000 6 800	73% 3 400 000 7 100	75% 3 800 000 7 800	
No 11 D S	54	F	Climacteric, secondary anemia colitis	Hgb 71% R B C 3 660 000 W B C 3 300			77% 4 070 000 4 300	70% 3 390 000 5 500	77% 3 680 000 5 200	General and steady improvement. Menstruated for first time in 10 years after the injections
				Hgb 74% R B C 3 550 000 W B C 5 800			77% 4 030 000 4 400	77% 3 740 000 5 500	74% 3 920 000 5 000	
				Hgb 75% R B C 3 550 000 W B C 5 700			77% 4 070 000 4 300	75% 3 800 000 5 000	77% 3 900 000 5 200	
No 12 J F	36	F	Broncho- pneumonia	Hgb 54% R B C 3 200 000 W B C 11 000					15th In- jection 90% 5 200 000 9,000	Rapid return of blood picture with unusual recovery of physical vigor. Case of Dr M Silberstein
No 13 M M	21	F	Secondary anemia	Hgb 60% R B C 3 225 000 W B C 6 200					81% 4 100 000 7 700	Marked improvement in energy able to resume work efficiently. Case of Dr Sidney F Friedman

TABLE I—Continued

Case	Age	Sex	Diagnosis	1st Injection	15th Injection	Comment
No 14 K	62	F	Post pneumonia debility	Hgb 45% R B C 2 900 000 W B C 5,200	69% 3 750 000 6 300	Patient felt stronger appeared fairly ruddy compared to extreme pallor at onset Case of Dr Sidney T Friedman
No 15 E A	51½	M	Pan sinusitis	Hgb 75% R B C 4 050 000 W B C 7 350	8th Injection 98% 4 390 000 8 350	Nervousness and irritability disappeared patient ate better Lost pesty look and pallor Case of Dr Sidney T Friedman
No 16	60	M	Asthma debility, anemic pallor	Hgb 54% R B C 4 600 000 W B C 7 200	10th Injection 80% R B C 4 800 000 W B C 9 400	Subjectively much improved not only from general debility but also from asthma Was more comfortable
No 17	32	F	Pregnancy 3 months Miscarriage	Hgb 45% R B C 2 800 000 W B C 6 200	12th Injection 80% 4 200 000 8 000	General condition very much improved

drop in blood pressure with slight sweating and vertigo. Some of the patients had slight tingling sensation in the extremities. The sensation of well being and feeling of increased energy were in excess of those ordinarily experienced from iron therapy alone.

Another noteworthy point was the fact that, although one and one-half grains of ferrous adenylyate was the calculated amount of daily iron needed, nevertheless, the dosage employed on the reported cases was only one-half grain of ferrous adenylyate. Thus, in terms of iron alone, would represent only 6 mg. The pronounced hemoglobin response is definitely out of all proportion to this quantity of iron and must represent the supporting action of the adenylic acid, either through its stimulation of the bone marrow, directly, or the improvement of the utilization of iron in the food. In this respect adenylic acid may be looked upon as one of the effective substances so stimulating to blood regeneration found in the various tissue extracts, such as liver, beef, and stomach. There are many factors pointing to this. First, that these tissues are a rich source of adenylic acid, second, that Williams has shown vitamin B to have a pyrimidine nucleus, thus relating this to the adenylic acid structure, and third, the findings of P. Karrer and H. V. Euler, who showed in their paper, on the water soluble growth vitamins of the B group, that the active substance obtained through the physical and chemical treatment of an aqueous liver extract showed spectroscopically a maximum absorption band at 260 mμ which agreed with that of cozymase and the adenylyl nucleotide. When one adds to this the findings of Rothmann, that the hemoglobin per cent and erythrocyte count bear a direct relationship to the amount of adenylic acid of the blood, one gets a striking view of the important relationship of the adenylic nucleotide to blood formation.

It is now commonly accepted, as shown by Bethell, "that the retarded rate of hemoglobin formation is most often due to a lack of iron, although such deficiency may possibly be associated with insufficient available protein, pigment complex, and certain vitamins"

Minot has strongly pointed out "that the term iron deficiency does not adequately describe all cases placed under this heading. The withdrawal from the tissues of material to make hemoglobin, the influence of substances on physiologic mechanisms for the utilization of iron and hemoglobin building substances must be studied further before there is final knowledge concerning iron deficiency anemias"

It thus becomes apparent that the use of simple iron compounds such as ferrous sulphate, ferric ammonium citrate, or reduced iron, such as have been used as far back as antiquity, may now be supplanted by the iron compounds of physiologically related radicals and supplemented specific active agents

The stimulation of bone marrow function, by the continued action of iron and nucleotide, was demonstrated in our cases by the elevation of the whole blood picture in every instance. The feeling of well being experienced by the patient could be compared with the sensation produced by the physiologic leukocytosis following ingestion of food, stimulation of a cold shower or massage. Also, the elevation of a white cell count from three thousand to five or six thousand lessens the danger of approach to the more malignant forms of neutropenia

BIBLIOGRAPHY

- BUELL, M. V., and PERKINS, M. E. Adenine nucleotide content of blood with a micro analytical method for its determination, *Jr Biol Chem*, 1928, lxxvi, 95-106
- BENNET, D. W., and DRURY, A. N. Further observations relating to the physiological activity of adenine compounds, *Jr Physiol*, 1931, lxxii, 288-320
- BETHELL, F. N. The application of diagnostic criteria to the treatment of the anemias, *N Y State Jr Med*, 1935, xxxv, 799-805
- DE CARO, L. Sull' Azione Biol Dell' Acido Adenilico Del Lievito, *Arch Sc Biol (Italy)*, 1931, xvi, 563-574
- DOAN, C. A. Neutropenia, *Jr Am Med Assoc*, 1932, 195
- DRURY, A. N., and SZENT-GYORGYI, A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart, *Jr Physiol*, 1929, lxxviii, 213-237
- EMBDEN, G., and LEHNARTZ, M. Über Phosphorsäureabspaltung aus Adenylsäure bei der Muskel-Kontraktion, *Klin Wchnschr*, 1930, ix, 937
- EMBDEN, and SCHMIDT, G. Über die Bedeutung der Adenyl für die Muskelfunktion, *Hoppe-Seyler's Ztschr f physiol Chem*, 1928-29, clxxvii
- EULER, H. VON, and MYRBOCK, K. Co-Zymase, zur Bestimmung der Co-Zymase, *Ztschr f physiol Chem*, 1931, cxviii, 219
- EULFR, H. VON, and MYRBOCK, K. Co-Zymase und Adenylsäure, *Ztschr f physiol Chem*, 1931, cxix, 189
- FULLERTON, H. W. Treatment of hypochromic anemia with soluble ferrous salts, *Edinburgh Med Jr*, 1934, vi
- HEATH, STRAUSS, and CASTLE. Quantitative aspects of iron deficiency in hypochromic anemia (the parenteral administration of iron), *Jr Clin Invest*, 1932, ii, 1293

- JACOBSEN, E. Investigations on in adenyle-pyro-phosphatase, Skand Arch Physiol, 1931, lxi, 90
- JACKSON, H., JR. Studies in nucleic metabolism, adenine nucleotide in human blood, Jr Biol Chem, 1923, lvi, 121-128
- KARRER, P., and EULER, H. V. Water soluble growth vitamins of the B group, Arkiv Kemi Mineral Geol, N B, 1933, No 16
- KAY, H. D., and MARSHALL, P. G. Phosphatase compounds of milk, presence of adenine nucleotide in milk, Biochem Jr, 1923, xxi, 416-418
- LEVENE, P. A., and BASS, L. W. Nucleic acids, 1931, New York
- LOHMANN, K. Über die Pyrophosphatfraktion im Muskel, Naturwissenschaften, 1929, xvi, 624
- MAYER, K. Über das Koferment der Milchsäurebildung im Muskel, Biochem Ztschr, 1931, ccxxxvii, 437-444
- MINOT, G. R. The anemias of nutritional deficiency, Jr Am Med Assoc, 1935, 1176
- OSTERN, P. Über die Purinkörper des Kaninchen-Muskels, Biochem Ztschr, 1930, ccxi, 64-70
- POHLE, K. Über das Vorkommen von Adenylsäure im Gehirn, Hoppe-Seyler's Ztschr f physiol Chem, 1929, clxxvi, 281-283
- ROBERTS, S. R., and KRACKE, R. R. Leukopenia, ANN INT MED, 1931, v, 40
- ROSENFELD, L. Über den Einfluss der Guaninyl- und Adenylsäure auf die Harnsäureausscheidung, Hoppe-Seyler's Ztschr f physiol Chem, 1924, cxlvi, 280-287
- ROTHMANN, H. Klinische Untersuchungen über die Adenosinphosphorsäure (Adenin-Nucleotid) in Blut und Galle, Zugleich ein Beitrag zur Frage der Entstehung der endogenen Harnsäure im menschlichen Organismus, Ztschr f d ges exper Med, 1931, lxxvii, 22
- RUSKIN, S. L. Nucleic acid and nucleotide therapy in nasal disease, Arch Otolaryng, 1935, xxii, 172-181
- RUSKIN, S. L. The mechanisms of nephrosis in sinusitis in children, Trans Third Internat Pediat Congr, Acta Pediat, 1933, xvi
- WEDD, A. M. The action of adenosine and certain related compounds on the coronary flow of the perfused heart of the rabbit, Jr Pharmacol and Exper Therap, 1931, xli, 355-366
- WILLIAMS, R. R. Structure of vitamin B, Jr Am Chem Soc, 1935, lvii, 229-230

HEPATIC COMPLICATIONS IN THE TREATMENT OF SYPHILIS

II INCIDENCE OF HEPATIC DISEASE IN PATIENTS WITH UNTREATED SYPHILIS AND DURING THEIR SUBSEQUENT TREATMENT

By FREDERICK KELLOGG, M D,† NORMAN N EPSTEIN, M D, and WM J KERR, M D, F A C P, *San Francisco, California*

HEPATITIS as a complication of anti-syphilitic therapy is not an uncommon occurrence. The injury thus suffered by the liver may be transient or it may be permanent, resulting in cirrhosis. Thus Baldridge¹ reported that, of a series of 36 patients with definite portal cirrhosis, one-third had histories of treatment for syphilis. During the past 10 years the value of controlling the arsphenamine treatment of syphilis by functional tests of the liver has been repeatedly emphasized. Such tests are indicated especially for patients with histories of hepatic disease or with evidence of disturbance of the liver developing during the course of treatment. Previous studies² have also shown that liver-function tests may reveal hepatic disease in a number of patients who present no clinical signs of liver dysfunction.

Consequently, it seemed desirable to survey a group of patients with untreated syphilis, and to follow these patients with repeated functional tests of the liver during their subsequent treatment. In this way it was hoped to determine (1) the incidence of hepatic disease in patients with untreated syphilis, (2) the effect of anti-syphilitic treatment on the liver, and (3) the possible relationship of diminished liver-function to untoward reactions resulting from treatment.

Method of Study The patients with syphilis who were selected for this study had received little or no antisyphilitic treatment. Some of these patients had received a few treatments with bismuth or mercury and a few had received one or two treatments with an arsphenamine. Thorough physical examinations were done on all patients, and complete histories were taken with special reference to antecedent disease of the liver. The liver-function of these patients was checked routinely with the Rose Bengal dye test at the onset of treatment, and at intervals during the course of therapy. This test has been used in the University of California Hospital the past 12 years, and has proved a reliable and satisfactory method of determining hepatic function. Details of the technic have been recently described,³ and will not be repeated here. A retention of over 55 per cent of the dye in the blood stream at the end of eight minutes, and of over 35 per cent of the dye at the end of 16 minutes, is considered to indicate abnormal hepatic func-

* Received for publication March 18, 1936

From the Division of Medicine and the Department of Dermatology, University of California Medical School, San Francisco

† Research Fellow, American College of Physicians

tion For the purposes of this study more stringent criteria were selected, and only patients with a retention of the dye of over 60 per cent at the end of eight minutes, and of over 40 per cent at the end of 16 minutes were considered to have abnormal hepatic function

Some of the patients with abnormal hepatic function were further tested for disease of the liver by the modified glucose tolerance test,⁴ and by determination of urobilin in the urine

Observations A total of 90 patients, on whom a total of 200 Rose Bengal tests were performed, was studied Unfortunately a large percentage of patients treated at this clinic are transient, so there were 39 patients on each of whom we were able to make only one test The remaining 51 patients had two to six tests each during the course of their treatment

Of the entire group, 57 were males and 33 were females The age distribution, shown in table 1, indicates that the greater number were between

TABLE I
Distribution of Patients According to Age and Sex

Entire Series							
Age	10-19	20-29	30-39	40-49	50-59	60-69	Total
Male	3	17	14	17	5	1	57
Female	2	9	10	7	4	1	33
Total	5	26	24	24	9	2	90

Group with Abnormal Hepatic Function before Treatment							
Male	0	1	2	8	3	0	14
Female	0	0	4	1	0	1	6
Total	0	1	6	9	3	1	20

20 and 50 years of age When grouped according to the diagnosis made at entry, 15 were in the primary stage, 23 were in the secondary stage, 35 were classified as latent, and 17 were classified as late—four of these latter having syphilis of the central nervous system

The incidence of abnormal liver function as indicated by the Rose Bengal test was surprisingly high Of the 90 patients in our series, 20 had abnormal liver-function before antisyphilitic treatment was given As shown in table 1, there was a tendency for this group to be of an older age than the group as a whole, but there was no definite correlation between the liver-function and the stage of the disease in these patients

Group with Repeated Tests, Normal Liver Function before Treatment Of the patients with normal hepatic function before antisyphilitic treatment, 33 had repeated tests during the course of therapy Five of these (table 2) were shown to have an abnormal test of liver-function while under treatment In two patients (numbers 2 and 5), the hepatic function was still

TABLE II
Patients Developing an Abnormal Retention of Rose Bengal Dye during the Course of Antisyphilitic Therapy

Case No	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min	16 min			
1	34	M	Latent syphilis	4-12-34	42	20	None	None	Urobilin absent in urine 5-10-35
				10-13-34	72	40	Slight	Neoarsph 4.5 gm	
				5-10-35	64	32	None	Neoarsph 9.0 gm	
2	29	M	Tabes dorsalis	10-22-33	60	27	None	Neoarsph 1.3 gm	Moderate alcoholic history
				3-2-34	69	41	Slight	Neoarsph 4.0 gm	
				7-14-34	32	24	None	Neoarsph 4.5 gm	
				6-17-35	72	37	Slight	Tryparsamide 38 gm	
3	45	F	Latent syphilis	9-3-34	51	28	None	None	Malaise following second treatment of neoarsphenamine. Urobilin absent in urine 5-6-35. Modified glucose tolerance test indicative of hepatic damage 6-5-35
				2-8-35	62	40	Slight	Neoarsph 3.5 gm	
				5-6-35	56	32	None	Neoarsph 0.9 gm	
4	41	M	Primary syphilis	3-7-34	48	24	None	Maphars 0.09 gm	Moderate alcoholic history. Mild hepatitis and glomerular nephritis while on therapy with bis-muth 9-10-34. Tolerated further treatment without reaction. Urobilin present in urine 5-13-35
				7-28-34	68	46	Moderate	Maphars 0.9 gm	
				10-13-34	54	28	None	None	
				5-13-35	56	26	None	Maphars 0.95 gm	
5	64	M	Latent syphilis	5-29-34		30	None	None	Urobilin absent in urine 5-6-35
				9-24-34	88	53	Moderate	Maphars 0.40 gm	
				5-6-35	67	43	Slight	Maphars 0.60 gm	

abnormal at the time of the last examination, antisyphilitic treatment apparently having led to permanent hepatic damage. In the other three patients the abnormality was transient, and subsequent arsphenamine therapy was tolerated without mishap, though one patient (number 4) had had an attack of jaundice and glomerular nephritis.

Group with Repeated Tests, Abnormal Hepatic Function before Treatment There were 18 patients in this group, which can suitably be divided into a sub-group of 9 (table 3) in whom the function returned to normal following antisyphilitic therapy, and the remaining 9 (table 4) in whom the function of the liver continued to be abnormal.

In table 3 we have included a group of patients who may have had syphilitic involvement of the liver, inasmuch as the hepatic function improved with antisyphilitic therapy, although one patient (number 6) showed further impairment of liver-function before improvement occurred. Three patients (numbers 6, 9 and 11) had transitory attacks of dermatitis, probably related to antisyphilitic therapy. In one patient (number 8), an abnormal reading was obtained when the Rose Bengal test was performed a few hours after an injection of neoarsphenamine. This may represent only a temporary toxic effect on the liver, for in the course of our study on other patients a similar relationship has not infrequently been noted.

Table 4 represents a group of patients with an abnormal hepatic function which persisted after a period of one to two years of antisyphilitic treatment. It is highly significant that an increased impairment of hepatic function occurred in four (numbers 19, 20, 21, and 22) of this group during the course of arsphenamine therapy. In one patient (number 19) who had developed icterus, a marked improvement in liver-function followed the cessation of arsenical treatment. One patient (number 22) developed purpura after each administration of neoarsphenamine but tolerated mapharsen without ill effect.

Group with Only One Rose Bengal Test As stated before, there were 39 patients on whom only one Rose Bengal test was done. No reactions to arsphenamine therapy occurred in these patients while attending the clinic. Two patients (table 5) had definitely abnormal hepatic function. One of these (number 24) had a decompensated cirrhosis of the liver. This patient was lost sight of before antisyphilitic treatment was given.

Relation of Abnormal Hepatic Function to Untoward Reactions of Therapy Eighty patients received treatment with the arsphenamines. Sixty-two of these patients had initially a normal liver-function, and 18 had abnormal function.

Table 6 shows the untoward reactions which occurred. Approximately one-fifth (12 patients) of the group with initial normal function manifested some degree of intolerance to arsenic at one time or another. The only serious reaction occurring was the jaundice and glomerular nephritis which one patient developed. Subsequently, this patient tolerated arsenical therapy without untoward effects.

TABLE III
Patients with Abnormal Retention of Rose Bengal Dye Initially, but with Normal Function following Specific Therapy

Case No	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min	16 min			
6	45	M	Secondary syphilis	5-1-33	62	38	Slight	Neosaph 1.2 gm	Several attacks of dermatitis questionably related to therapy. Modified glucose tolerance test indicative of hepatic damage 7-26-33
				6-26-33	76	52	Moderate	Neosaph 3.4 gm	
				10-25-33	62	38	Slight	Neosaph 3.3 gm	
				6-18-34		24	None	Neosaph 4.7 gm	
7	44	M	Latent syphilis	4-17-34	66	43	Slight	None	Slight alcoholic history. Icterus index 7 on 5-13-35. Urobilin absent in urine 5-13-35
				5-13-35	57	29	None	Maphars 0.92 gm	
8	21	M	Secondary syphilis	5-29-33	70	40	Slight	Neosaph 0.45 gm	Rose bengal test performed 4 hours after first treatment with neosaph
				7-24-33	46	20	None	Neosaph 3.5 gm	
9	52	M	Late syphilis	5-22-33	68	43	Slight	None	Dermatitis questionably related to therapy with bismuth. Urobilin present in urine 5-22-33 and 5-3-35
				8-21-33	67	34	None	None	
				10-2-33	53	29	None	None	
				10-4-34	65	43	Slight	None	
				5-3-35	56	33	None	Neosaph 3.1 gm	
10	33	F	Primary syphilis	8-13-34	68	43	Slight	Maphars 0.11 gm	Icterus index 6 on 6-28-35
				2-25-35	63	35	Slight	Maphars 0.55 gm	
				6-28-35	52	24	None	Maphars 0.36 gm	
11	49	M	Latent syphilis	3-28-34	70	40	Slight	None	Transient dermatitis following neosaph 12-15-34
				10-22-34	59	35	None	Neosaph 1.1 gm	
				3-18-35	66	34	None	Neosaph 4.7 gm	

TABLE III—Continued

Case No	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min	16 min			
12	43	M	Latent syphilis	1-17-34	64	46	Moderate	None	Liver slightly enlarged ance test indicative of hepatic damage 6-17-35
				4-16-34	68	44	Moderate	None	
				9-28-34	57	37	Slight	Neosarsph 3.5 gm	
				2-8-35	62	40	Slight	Neosarsph 4.8 gm	
				4-1-35	56	34	None	Neosarsph 4.7 gm	
13	47	M	Latent syphilis	1-8-34	80	48	Moderate	None	Urobilin present in urine 8-9-35
				3-7-34	52	28	None	Neosarsph 0.3 gm	
				10-1-34	76	35	Slight	Neosarsph 3.5 gm	
				2-25-35	56	33	None	Neosarsph 4.5 gm	
14	32	F	Latent syphilis	6-12-33	61	36	Slight	None	Strong alcoholic history Liver slightly enlarged
				2-18-35	64	41	Slight	Neosarsph 10.0 gm	
				8-9-35	56	30	None	Maphars 0.32 gm	
15	35	M	Recurrent secondary syphilis	4-4-34	58	38	Slight	None	
				2-18-35	66	40	Slight	Neosarsph 9.0 gm	
				8-20-35	54	27	None	Neosarsph 4.0 gm	

TABLE IV
Patients with Initial Abnormal Liver Function Which Is Unaltered or Made Worse by Antisyphilitic Therapy

Case No	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min	16 min			
16	41	M	Secondary syphilis	5-15-33	60	36	Slight	Neosarsph 0.9 gm	Slight alcoholic history 1928 Icterus index 11 on 8-2-33 Urobilin absent in urine 5-3-35
				10-24-33	56	34	None	Neosarsph 5.4 gm	
				9-28-34	63	40	Slight	Neosarsph 11.7 gm	
				5-3-35	70	35	Slight	Neosarsph 4.6 gm	
17	66	F	Latent syphilis	3-2-34	64	40	Slight	None	Modified glucose tolerance test indicative of hepatic damage 6-17-35
				10-4-34	55	37	Slight	None	
				3-11-35	57	34	None	Neosarsph 2.1 gm	
				6-14-35	60	42	Slight	None	
18	38	F	Primary syphilis	4-24-34	78	50	Moderate	None	Malaise following first treatment of mapharsen
				2-26-35	76	44	Slight	Maphars 0.76 gm	
19	44	M	Latent syphilis, cirrhosis	6-26-33	76	52	Moderate	None	Moderate alcoholic history Slightly enlarged liver Urobilin present in urine 6-26-33 Modified glucose tolerance test indicative of hepatic damage 7-26-33 Icterus present October 1934 to March 1935
				7-24-33	83	57	Marked	None	
				11-21-33	71	48	Moderate	None	
				10-4-34	91	77	Marked	Neosarsph 3.6 gm	
				3-1-35	80	60	Marked	Neosarsph 4.6 gm	
				6-18-35	60	44	Slight	None	

TABLE IV—Continued

Case No	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min	16 min			
20	33	M	Recurrent secondary syphilis	3-2-34 4-24-34 5-3-35	60 56 76	36 34 50	Slight None Moderate	None Maphars 0.31 gm Neosarsph 4.0 gm	Urobilin present in urine 5-3-35
21	50	M	Latent syphilis	4-24-34 10-8-34 2-1-35	60 59 80	40 39 60	Slight Slight Marked	None Neosarsph 3.5 gm Neosarsph 4.0 gm	Received neosarsphenamine 4 hours before Rose Bengal test 2-1-35
22	48	F	Syphilis of the CNS	6-26-33	69 67 63	40 34 47	Slight Slight Moderate	None Neosarsph 1.0 gm {Neosarsph 0.15 gm (Mapharsen 0.26 gm	Nausea following first treatment with neosarsphenamine Subcutaneous ecchymoses following all subsequent treatments of neosarsphenamine No reaction to mapharsen Urobilin absent in urine 5-6-35 Modified glucose tolerance test indicative of hepatic damage on 7-6-33 and 6-5-35
23	59	M	Latent syphilis	2-20-34 8-9-35	80 88	42 56	Moderate Marked	None None	No arsenical treatment Received bismuth and mercury

TABLE V
Patients with Abnormal Initial Hepatic Function, Subsequent Rose Bengal Tests not Performed

Case No	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min	16 min			
24	39	F	Latent syphilis, cirrhosis	10-24-33	78	68	Marked	None	Strong alcoholic history 4 years Edema of ankles and slight icterus for 3 months Liver greatly enlarged No arsenical treatment
25	44	M	Secondary syphilis	8-13-34	78	38	Slight	Maphars 0.10 gm	Received mapharsen 1.44 gm without reaction

TABLE VI
Reactions during Course of Antisyphilitic Therapy

	Abnormal Rose Bengal Test before Treatment	Normal Rose Bengal Test before Treatment	Total
Total number receiving the arsphenamines	18	62	80
Reactions			
Dermatitis (mild)	3	4	7
Malaise	2	7	9
Jaundice	1	1	2
Purpura	1	0	1
Enlarged liver before treatment	3	7	10

Seven (approximately one-third) of the group with initial abnormal function developed untoward reactions. Two had serious reactions, one having jaundice and the other purpura. Although the series is not large enough to be statistically significant, it would appear that patients with abnormal hepatic function are more apt to develop untoward reactions than are patients with normally functioning livers.

Comment. The findings presented demonstrate that latent hepatic disease is not uncommon in patients with untreated syphilis. Of the entire series of 90 patients, 20 were found to have abnormal liver-function as shown by protracted retention of Rose Bengal dye in the circulation. Two of these patients had other clinical evidence indicative of cirrhosis of the liver, and a third patient had a history of jaundice. The remainder, 17 in number, had impaired liver-function which was detected only by the Rose Bengal test. In 10 of these 17 patients improvement in hepatic function followed specific therapy, while in the remaining seven, the liver-function remained abnormal in spite of long continued antisyphilitic therapy. Improvement in the patient's syphilitic condition probably accounts for the improvement in the liver-function in the first 10 while in the other seven the liver disease was probably so advanced that the function could not be restored. It is in this group where extreme caution must be exercised in the administration of the arsphenamines as irreparable harm may be done by these drugs.

Only one patient (table 4, number 19) with clinically recognizable cirrhosis of the liver received arsenical therapy. This was tolerated poorly, and jaundice developed which subsequently disappeared only after treatment with arsphenamine was discontinued. The patient (table 4, number 16) with a history of jaundice suffered no untoward effects from treatment. Six of the seven patients with presumably latent cirrhosis were given the arsphenamines cautiously. This was well tolerated except for one patient (table 4, number 22) who developed purpura following neoarsphenamine. In two other patients (table 4, numbers 20 and 21), antisyphilitic therapy led to increased hepatic damage as shown by the Rose Bengal test.

Of the 29 patients with an initial normal hepatic function test, five developed hepatic injury as shown by the Rose Bengal test. This damage was slight to moderate, and relatively transient. One patient (table 2, number 4) developed jaundice and glomerular nephritis temporarily, but subsequently tolerated arsenical treatment without reaction. Since the development of cirrhosis is a relatively slow process, a further study of these patients is indicated to determine the possible relationship of anti-syphilitic therapy to the future course and end result.

An analysis of the untoward reactions occurring during antisyphilitic therapy suggests that patients with an abnormal hepatic function are more apt to suffer ill effects than those with normal liver-function. If this is borne out by further observations, it would be advisable to perform routine liver-function tests on all patients with syphilis before instituting therapy. Every effort should be exerted to protect the liver from the harmful effects of antisyphilitic remedies. We would suggest the taking of carbohydrates by mouth a few hours before the administration of an injection of arsphenamine and caution the patient against the taking of alcohol or an excess of fat in his diet.

SUMMARY

1 A high incidence (19 per cent) of abnormal liver-function, as shown by the Rose Bengal test, was found in a group of 90 patients with untreated syphilis.

2 Antisyphilitic therapy caused transitory disturbances in liver-function in five of 29 patients originally having a normal function, and caused further impairment in four of 18 patients with initial abnormal function.

3 Patients with initially abnormal liver-function had an increased tendency to have untoward reactions to antisyphilitic therapy.

BIBLIOGRAPHY

- 1 BALDRIDGE, C. W. The relationship between antisyphilitic treatment and toxic cirrhosis, *Am J Med Sci*, 1934, **CLXXXVIII**, 685.
- 2 BISKIND, G. R., EPSTEIN, N. N., and KERR, W. J. Hepatic complications in the treatment of syphilis, *Ann Int Med*, 1934, **VII**, 966.
- 3 ALTHAUSEN, T. L., BISKIND, G. R., and KERR, W. J. The Rose Bengal test of hepatic function, a spectroscopic method, *Jr Lab and Clin Med*, 1933, **XVIII**, 954.
- 4 ALTHAUSEN, T. L., GUNTHER, L., LAGFN, J. B., and KERR, W. J. Modification of the dextrose tolerance test as an index of metabolic activity of the liver, *Arch Int Med*, 1930, **XLVI**, 482.

NEUROLOGICAL SYMPTOMS IN POSTHEMORRHAGIC SECONDARY ANEMIA¹

By SAMUEL B. HADDEN, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

In 1878 the pathological picture of postero-lateral-sclerosis was described by Kahler and Pick,¹ and in 1887 Lichtheim² pointed out the frequency of the relationship of this neurological condition to pernicious anemia. At the present time the symptom complex of postero-lateral-sclerosis is regarded as most commonly the result of primary pernicious anemia. The relationship of secondary anemias to changes in the nervous system, however, is less well known. Changes in the cord occurring in secondary anemia have been reported, but not all these cases can be accepted as authentic.

Oppenheim³ believed that in all cases of postero-lateral-sclerosis the anemia need not be pernicious, and he reports one case in which the postero-lateral-sclerosis was the result of the cachexia due to a malignant tumor, one occurring during the anemia of lactation, and three cases in persons in the sixth and seventh decade of life who had an anemia he attributed to chronic malaria which was contracted in early life. These cases were reported before our present knowledge of pernicious anemia and cannot be accepted as due to secondary anemia without question, although many German neurologists in the past have likewise held the opinion that secondary anemia may cause changes in the nervous system.

Sargent⁴ reports cases of simple achlorhydric anemia where symptoms of postero-lateral-sclerosis existed and in whom marked improvement of both the blood picture and nervous symptoms occurred from the use of iron, but not from liver therapy. This worker believes that in all types of anemia, including pernicious, the nervous symptoms are more promptly and effectively improved by massive doses of iron than by liver therapy alone. All of his cases received at least 150 grams of Bland's mass each day.

The view that the anemia is not the main factor in the production of the postero-lateral-sclerosis of primary pernicious anemia is based upon the fact that many times the nervous symptoms long precede the anemia. Spiller⁵ has long held this opinion. Castle⁶ states that pernicious anemia is the result of the absence of a specific intrinsic factor of gastric origin. Nervous system symptoms associated with achylia gastrica are not infrequent, notably in pellagra. In tapeworm and hookworm anemias, and in the anemia of sprue nervous system symptoms are encountered, but they may be the result of the toxic factors of the disease and not due to blood impoverishment alone.

In many of the dietary deficiency diseases there is an associated anemia with nervous symptoms, but the magnificent work of Mellanby⁷ tends to prove that here again the anemia cannot be considered the important factor.

* Received for publication September 20, 1935

In all his experimental animals he could demonstrate diminution or depletion of the vitamin A content of the liver, and by the addition of vitamin A or carotin to the diet he was able to prevent degenerative changes in the nervous system. It is of interest that in some cases of postero-lateral-sclerosis of pernicious anemia in humans he found decrease in the amount of vitamin A in the liver. This was not a constant finding, but even the presence of vitamin A in the body does not rule out its faulty utilization.

Weil and Davidson,⁸ in their exhaustive pathological studies on the spinal cord in anemia, concluded that postero-lateral-sclerosis probably never occurs in any secondary anemia. In their series of cases of secondary anemia, changes in the cord were noticed in a few in which the differentiation between primary and secondary anemia was not clear. They do not consider any other changes in the central nervous system than cord changes and include in their group of secondary anemia all cases with 75 per cent hemoglobin or less and 3,500,000 red blood cells or less. In only eight of their cases of secondary anemia, not including the four leukemias, was the red blood cell count under 2,500,000, and in only six cases was the hemoglobin under 50 per cent. In one of these cases involvement of the column of Goll was noted in a patient who died of tuberculous meningitis. The hemoglobin in this case was 28 per cent. In their cases of secondary anemia which showed central nervous system lesions, these lesions were usually the result of metastatic or myelitic lesions. In this paper of Weil and Davidson the number of really severe cases of secondary anemia is too few to warrant their conclusion that cord changes do not occur in secondary anemia. In the 10 cases of primary pernicious anemia used in their paper, in only two was the hemoglobin above 50 per cent or the red blood cell count above two million, so that aside from the toxic factor their pernicious anemia cases represented much more severe red blood cell and hemoglobin deficiency than their secondary anemia cases.

The cases of anemia with nervous symptoms which I present in this paper are very severe cases, in which there was rapid diminution of the hemoglobin and red blood cells by massive hemorrhage from medical or obstetrical causes to almost fatal levels.

CASE REPORTS

Case 1 The first case was from my service at the Episcopal Hospital. Briefly, the patient, a woman, aged 40, suffered from severe postpartum hemorrhage March 1, 1927. She was in a stuporous state for several days following delivery and complained of blindness and a cold, numb feeling of the body, especially in her lower extremities. It was several weeks before her vision returned to what she considered normal. On getting out of bed she experienced considerable difficulty in walking because she "could not tell the position in which she placed her feet and had to watch the ground constantly." The patient states, and her friends confirm the statement, that the hemorrhage was so severe that coal shovels and buckets were used to scoop up the clots after her delivery, so there can be no question that the loss of blood was unusually large although no blood studies were made at the time. At

the time of her observation at the Episcopal Hospital, during November and December 1932, the patient showed a suggestion of nystagmus, incoordination in finger-to-nose test, marked pyramidal tract and posterior column symptoms, diminution of visual acuity with evidence of old optic atrophy, concentric contraction of visual fields, normal gastric analysis and blood picture. Colloidal gold showed a low first zone alteration.

Case 2 A S was reported clinically by Dr W L McConnell⁹ in January 1907, and is included through the courtesy of Dr William G Spiller from his service at the Philadelphia General Hospital. The patient was admitted Dec 12, 1903. At the time of admission the first blood examination revealed a hemoglobin of 16 per cent and 1,750,000 red blood cells. A few days before admission the patient, while in the county prison, had had a massive gastric or pulmonary hemorrhage. He had been in poor health previously. The following day he noticed dimness of vision. His sight gradually failed until one week after the hemorrhage vision was lost in both eyes. Shortly after the hemorrhage he experienced weakness in both legs and eventually entirely lost his ability to walk. Power in his legs, however, was never entirely lost. Three months after the weakness in his legs he began to experience weakness in both upper extremities. Improvement was very gradual and approximately 10 months later he was able to stand and walk a bit, although extremely ataxic. The following is a summary of notes made by Dr Spiller on Aug 4, 1904: "No facial weakness or nystagmus. The upper limbs are wasted. It is difficult to say whether there is any greater wasting in one part than the other. The biceps tendon reflex is present on each side though not very pronounced. Sensation in the upper extremities is normal. There is ataxia in the finger-to-nose test. Talipes-equinus varus on each side. Voluntary power in lower limbs fair at knees, but almost lost at ankles, very feeble in all parts of lower limbs. Lower limbs extremely wasted in all parts. Abnormal position of feet readily overcome passively. Patellar reflex feeble on the left side and detected by a slight contracture of the muscles. The right patella reflex is completely lost. No Achilles, Babinsky distinctly present on each side. The patient is unable to stand. Sensory examination negative."

The following table shows the gradual recovery from the severe anemia on admission.

TABLE I

Date	Hemoglobin	Red Blood Cells	White Blood Cells
	Percentage		
12/23/03	24	2,100,000	4,600
1/4/04	35	2,450,000	5,800
1/13/04	44	2,720,000	1,400
1/27/04	48	2,700,000	4,000
2/27/04	41	2,370,000	4,300
3/5/04	44	3,000,000	5,400
4/12/04	62	3,350,000	5,500
5/18/04	85	4,630,000	5,600
8/30/04	76	5,760,000	8,000

It will be noted it was about six months before his blood reached approximately a normal level. His condition remained grave for some time, but gradually he improved. Loss of vision was permanent. For many years signs of pyramidal tract involvement persisted but eventually he was able to walk without any great difficulty. The last neurological examination of merit was by Dr Fassey on October 14, 1921, and his findings are chiefly negative. Patient was blind, he presented no definite disturbance of gait or station, no sensory disturbance, tendon reflexes were all active and equal, with normal plantar reflexes. Free HCl was diminished and on one examination absent.

In 1924 the patient had a "stroke" and died a few days following it

Pathologically the brain presented multiple areas of softening with advanced arteriosclerosis. The cord was flat and granular. These diagnoses were confirmed microscopically, and in the cord mild bilateral pyramidal tract degeneration was noted. Degeneration of the optic nerves was advanced. General autopsy showed moderate arteriosclerosis and broncho-pneumonia.

It is unfortunate that the cerebral softening complicated this case as the pathological findings are lessened in importance thereby, but there is little doubt of the gravity of the symptoms which date their onset from his severe posthemorrhagic anemia.

Case 3 E. B., female, aged 39, admitted to the service of Dr. Girvin, Presbyterian Hospital, March 14, 1932, discharged June 5, 1932. The patient had been having prolonged menstrual periods with profuse bleeding over a period of two years each period lasting from three to 14 days and always being excessive. Fifteen days prior to her admission she had profuse bleeding with actual gushing at times. She was confined to bed four days prior to admission because of weakness and passed large vaginal clots. At the time of her admission she was extremely weak. The skin and mucous membranes were definitely blanched. Her blood pressure was 100 mm of mercury systolic and 44 mm of mercury diastolic. Vaginal examination revealed a soft cervix, four fingers dilated through which a soft round mass was being expelled. A tentative diagnosis of incomplete abortion was made. Her temperature was 99.2, pulse 132 per minute, pupils equal, moderately dilated and reacted to light. The heart was enlarged slightly to the left, sounds distant, rhythm regular, and a systolic murmur was heard at the apex. Her hemoglobin on admission was 45 per cent, red blood cells 1,880,000, leukocytes 22,000.

The patient began to bleed profusely at midnight of the day of admission. The following morning she was given 300 cc of citrated blood and 2,500 cc of saline. On March 15 an attempt was made to evacuate the uterus under nitrous oxide anesthesia, but the bleeding was so profuse that the attempt was stopped. In the next few days the patient became extremely drowsy, confused, and was aroused only with some difficulty, and four days after admission became definitely blind and had little more than light perception. She was transfused as follows: March 15, 300 cc blood, March 22, 500 cc, March 25, 375 cc. On March 19, when I first saw the patient, she was confused, blind and had a definite increase of muscular rigidity resembling a mild Parkinsonism, with some twitching movements, especially in the lower extremities. Her reflexes were all extremely hyperactive, but no Babinski was noted. Mental state was such that sensory examination was impossible. Again, on the twenty-first the patient was able to see objects moving in front of her eyes, but not distinctly. At this examination, with Dr. Cadwalader, there appeared to be evidence of very definite contraction of her visual field. The pupils reacted very slowly to light. There was no paralysis noted. Her reflexes were active and there was a suggestion of ankle clonus on both sides. The twitching movements previously noted were largely confined to the lower extremities and were irregular in nature. Gnostic sensations in the lower extremities were impaired. April 3 a note was made that there was a suggestion of paralysis of the upward associated ocular movements. Her expression was fixed. There was considerable rigidity with a suggestion of catatonia. Her general appearance suggested a developing Parkinsonian state. Her vision improved slowly but steadily, and by April 4, one month after admission, Dr. Langdon stated that central vision tested with a card was about one-third of normal. On May 6 the patient's general condition having improved remarkably, hysterectomy and appendectomy were performed by Dr. Laws and the patient was found to have an adenomyoma of the cervix of the uterus. At the time of her discharge from the hospital the patient's vision was normal in the left eye, with 6/12 vision in the right eye. Nerve heads were very pale and the visual fields were concentrically contracted.

This case is most interesting because of the fact that recovery from severe symptoms was apparently almost complete. Her hemoglobin three days after admission to the hospital had dropped to 27 per cent, with 1,200,000 red blood cells. After that, as a result of transfusions of some 2,000 c.c., the patient improved rapidly and these severe symptoms disappeared. The symptoms at the time of admission are remarkably like those of the first two cases. Only the prompt restoration of her blood by transfusion enabled this patient to survive and be restored. At the present time Dr. Langdon reports that her corrected vision is normal, but the visual fields are contracted. No recent neurological examination has been made.

In all three of these cases disturbance of vision was profound early in the course of their illness. Reports of transient and permanent blindness are not uncommon following hemorrhage. Hayes¹¹ in Norris and Oliver's "System of Diseases of the Eye" reports 11 cases following hemorrhage, 10 after gastric hemorrhage and one after hemorrhoidal bleeding. It is interesting to note that in all of these cases the hemorrhage was from a medical cause. Larrey,¹² in his medical memoirs of Napoleonic campaigns, in his discussion of diseases of the eye does not mention a single case of this sort, and the post World War literature does not reveal similar cases although massive hemorrhage was very common. Soldiers are usually in excellent health, and recovery from surgical hemorrhage is usually prompt.

It is interesting to theorize on the basis of the disturbances of the nervous system following a severe hemorrhage. The circulation apparently is kept adequate in the vital structures. The peripheral capillary bed is constricted with the resulting cold, pale skin and the common paresthesias. McGuigan and Atkinson¹³ have shown that hemorrhage remarkably increases the response of the peripheral sympathetics to adrenalin. It appears that as long as this vasomotor constrictor action continues the blood is kept in vital parts, but should there be vasomotor relaxation the blood then enters the less vital parts, and changes may occur in the nervous system.

During anemia the resulting anoxemia, as shown by the work of Landis,¹⁴ favors the development of edema with resulting impairment of function. Should this edema continue over a sufficient period of time permanent damage is sure to result, as in cases 1 and 2. Hemorrhagic anemia develops quickly, and there is little time for adjustment, so that anoxemia rapidly occurs with almost immediate disturbance of function of many portions of the nervous system. In all three cases there was profound disturbance of vision, locomotion and gnostic sensation very shortly after the massive hemorrhage. In cases 1 and 2 some of the symptoms were permanent and severe, while in case 3, where the oxygen carrying power of the blood was quickly restored by transfusion, recovery to almost normal health rather quickly occurred. The suggestive Parkinsonism and visual disturbance improved more slowly than other symptoms, possibly because the cells involved are more susceptible to anoxemia.

In secondary anemias from the slow loss or destruction of blood, symptoms of disturbance of nerve function are seldom a prominent feature, but are fairly constant. Visual disturbances, numbness, tingling and feelings

of coldness, generalized weakness, syncope, and rapid fatigue, resembling myasthenia gravis, are at times noted. In these cases blood is kept in the vital structures because the vasomotor control slowly adjusts itself. Unless the anemia is relieved, a sudden decompensation of the vasomotor system may occur and the vital centers be deprived of blood with resultant death. The brain and spinal cord in these cases show little more than intracellular changes because death occurs before more extensive damage can take place. In cachectic cases a comparatively small hemorrhage may be fatal because the already taxed vasomotor control suddenly decompensates.

CONCLUSIONS

1 Secondary anemia, especially posthemorrhage anemia, may produce organic alteration in the nervous system the optic nerves and pyramidal tracts being most commonly involved. Disturbance of gnostic sensation may occur from anoxemia of nerve endings and not be permanent.

2 Prompt restoration of oxygen carrying power of the blood is necessary to prevent the described symptoms from being permanent.

BIBLIOGRAPHY

- 1 KAHLER, O, and PICK, A. *Über kombinierte System-Erkrankung des Rückenmarks*, Arch f Psychiat, 1878, viii, 251.
- 2 LICHTHEIM, L. *Zur Kenntnis der perniciosen Anämie*, Verhandl d Cong f inn Med, Wiesb, 1887, vi, 84-99.
- 3 OPPENHEIM, H. *Textbook of nervous diseases* (translated by Alex Bruce), 1911, Vol 1, pp 188-189, Otto Shulze and Co, Edinburgh.
- 4 SARGANT, W, and LANGMEAD, F S. *Treatment of nervous disorders accompanying anemia by intensive iron therapy*, Lancet, 1932, ii, 1322-1326.
- 5 SPILLER. *Personal Communication*.
- 6 CASTLE, W B, TOWNSEND, W C, and HEATH, C W. *Am Jr Med Sci*, 1930, clxxx, 305-335.
- 7 MELLANBY, E. *Experimental production and prevention of degeneration in the spinal cord*, Brain, 1931, liv, 247-290.
- 8 WEIL, A, and DAVIDSON, C. *Changes in the spinal cord in anemia—clinicomicroscopic study*, Arch Neurol and Psychiat, 1929, xlii, 966-1000.
- 9 McCONNELL, J W. *Spinal cord changes following a secondary general anemia, with recovery*, Jr Nerv and Ment Dis, 1907, xxiv, 658-659.
- 10 LANGDON, H M. *Amaurosis after uterine hemorrhage*, Arch Ophth, 1933, x, 99-102.
- 11 HAYES, in NORRIS and OLIVER'S *System of diseases of the eye*, 1897, Vol II, J B Lippincott, Philadelphia.
- 12 LARREY. *Observations on wounds and their complications by erysipelas, gangrene and tetanus and principal diseases and injuries of the head, ear and eye* (translated by E F Rivinus).
- 13 MCGUIGAN, H, and ATKINSON, H V. *The effect of hemorrhage on the sympathetic nerves*, Am Jr Physiol, 1921, lvii, 95-103.
- 14 LANDIS, E M, JONAS, L, ANGEVINE, M, and ERB, W. *The passage of fluid and protein through the human capillary wall during venous congestion*, Jr Clin Invest, 1932, xi, 717-734.

CASE REPORTS

ADENOMA OF THE PARATHYROID GLAND, WITH HYPERPARATHYROIDISM *

By SAMUEL S RIVEN, M D, F A C P, and MORTON F MASON, P H D,
Nashville, Tennessee

DURING the past ten years great advances have been made in knowledge of the function of the parathyroid glands. Hypoparathyroidism, with the associated disturbance of calcium metabolism, is an important cause of tetany. Oversecretion of the hormone of the parathyroid glands (hyperparathyroidism) causes decalcification of bone, hypercalcemia, hypophosphatemia and increased calcium and phosphorus excretion in the urine. This condition results in the development of generalized *ostitis fibrosa cystica*. In most instances of hyperparathyroidism the changes in the skeletal system are the principal features, but occasionally, as in the case to be reported, renal symptoms predominate, and failure to recognize this fact may lead to error.

CASE REPORT

Mrs E R, a 51 year old white female, was admitted to Vanderbilt University Hospital on April 29, 1935, complaining of pain in the left flank. The pain radiated around the abdomen, down to the genitalia and was associated with burning on urination. Seventeen years ago she had intermittent attacks of bilateral renal colic which lasted for nine months, associated with the passage of several small, dark brown stones. There were no more attacks until January 1935. During the first illness she was advised to discontinue eating meat, and, while on a low protein diet, developed sore tongue, roughness of the skin and swelling of the ankles. Because of these symptoms and pain in the back and lower extremities, she came to one of us on May 3, 1933. Roentgenograms of kidneys, left knee joint and left femur showed only thinning of the bones. The diagnoses of Paget's disease and nutritional edema were made and she was placed on a diet high in protein. On October 6, 1934, she returned because of swelling of the ankles, fatigue, nausea, vomiting, frequency of urination and nocturia. The urine contained some albumin and many pus cells. A serum calcium determination at this time was 13 milligrams per 100 cc†. Because of the hypercalcemia and the roentgen-ray findings of decalcification of the long bones, the patient was placed on a high calcium, high vitamin, high protein diet. Three months later she developed an attack of renal colic, and from January to April 1935 had three such attacks. The patient grew progressively weaker, her appetite became poor, and she lost 15 pounds in weight. In addition, she had cardiac palpitation brought on by nervousness and exertion.

* Received for publication February 19, 1936

From the Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville

† Normal serum calcium is 9 to 11 milligrams per 100 cc blood

Past History She had had scarlet fever at five years of age, influenza in 1918, and two or three attacks of sore throat. Her tonsils and appendix were removed 17 years ago. Her husband, one brother and one sister all have tuberculosis. She has had no symptoms of tuberculosis and repeated roentgenograms of the chest have been negative.

Physical Examination Physical examination revealed a rather flabby, malnourished, apathetic individual, normally developed. She was very intelligent. The head was peculiarly pointed in shape, the cheeks had a hollow, sunken appearance, and the chin protruded forward. The pupils reacted normally to light and accommodation, the fundus examination showed some variation in the retinal arteries, but there were no hemorrhages or exudate. There was fullness over the thyroid gland but no masses were palpable. The heart and lungs were normal. The blood pressure was 120/74 mm of Hg. Examination of the abdomen revealed distinct tenderness in the left flank. There was definite kyphosis of the dorsal spine and tenderness over the bones of both lower extremities. Pitting edema of the feet and ankles was present extending half-way up the legs.

Laboratory Data Urinalysis Specific gravity varied from 1.005 to 1.012, no albumin, sediment contained five to six red blood cells and an occasional white blood cell, the benzidine test was positive. Blood The red blood cell count was 3,760,000, hemoglobin 13 grams, white blood cell count 13,000. The blood smear was normal. Wassermann and Kahn tests were negative. The basal metabolic rate was minus 9 per cent. The phenosulphophthalein renal function test (intravenous) was 55 per cent. The blood non-protein nitrogen varied between 25 and 41 milligrams per 100 c.c. The serum phosphatase was 7 units per 100 c.c.* The serum protein was 6.8 per cent, with 4.3 per cent albumin and 2.5 per cent globulin. The serum calcium was 12.9 to 13.5 milligrams per 100 c.c. The serum inorganic phosphorus was 2.1 to 3 milligrams per 100 c.c. Roentgen-ray examination revealed a large ureteral calculus in the upper segment of the left ureter. "The wing of the left ilium showed marked thickening with striations and also a large area of osteitis in the left sacro-iliac region. There was considerable hypertrophic arthritis of the lumbar spine. There was marked thickening of the bones of the skull. The bones of the hand showed marked thinning of the cortex" (Dr. C. C. McClure). Because of the apparent disturbance in calcium metabolism, it was decided to investigate this more fully. The calcium metabolism was studied as follows. The patient was put on a low calcium diet containing 0.3 grams of calcium per day. After five days on this diet the whole of the urine and feces were collected for a three day period, the former as separate 24 hour specimens, and the calcium content of these was determined. Before commencement of the test period, and at the conclusion of the period, the patient received cachets of carmine, the appearance of the dye in the feces serving as an indicator for the demarcation of the period of observation. The total output of calcium for the three day period was 1,335 milligrams, of which 931 milligrams appeared in the urine and 424 appeared in the feces. In other words, 70 per cent of the total amount of calcium excreted appeared in the urine†. This study was repeated twice with similar results.

Diagnosis The skeletal decalcification, polyuria, nycturia, hypercalcemia, hypophosphatemia and calcium metabolism studies indicated the presence of hyperparathyroidism. An exploratory operation was done on May 29, 1935, with the expectation of finding an adenoma of a parathyroid gland or parathyroid hyperplasia. Dr. Barney Brooks found a parathyroid tumor 2.5 cm. in length and 1 cm. in diameter in the region of the left lower lobe of the thyroid. (Figure 1)

Pathological Report The specimen was a very soft, dark purple, club-shaped, smooth encapsulated tumor. A thin capsule was opened and a layer of blood was

* Normal serum phosphatase is 6 to 12 units per 100 c.c. blood.

† In a normal individual on a similar diet, only 10 to 30 per cent of the total calcium excreted appears in the urine, the remaining 70 to 90 per cent being present in the feces.

released. This revealed a brownish-yellow, dull, smooth tumor mass about one-half the size of the specimen. On cut section it had a smooth, homogeneous appearance and was light caramel in color. Dr. Goodpasture's report on the section was as follows: "The microscopic section consists of a very cellular, irregularly elliptical



FIG 1 Adenoma of the parathyroid gland

piece of tissue measuring 12 by 5 millimeters. Nuclear material as compared with cytoplasm is very abundant so that the tissue stains deeply blue with hematoxylin-eosin. Under low power the tissue seems to be quite uniform in appearance, consisting of epithelial cells arranged in small acini and alveoli compactly situated with very

little stroma and a rich collapsed capillary bed separating them. There are several medium-sized arteries and veins tracing through the substance of the tissue. The composition of the tissue is not entirely uniform because there are several areas situated toward the center of the mass which are less cellular than the surrounding tissue and in which the alveoli are thinned out and often arranged in strands. Here the nests of epithelial cells are widely separated by spaces containing a pink granular precipitate. These spaces appear to be greatly distended lymphatics. In other foci the epithelial cells are compact but contain a relatively abundant pink-staining granular cytoplasm, so that these areas have a paler pinkish appearance in contrast to the denser surrounding areas. Where the alveoli have an acinar arrangement the epithelial cells are low cuboidal in shape and their nuclei are situated toward the basement membrane. Throughout the section the cytoplasm of the cells is faintly pink, containing amorphous granular material and sometimes the cytoplasm appears to be washed out, but in general the epithelial cells throughout the section have irregular basophilic condensations within the cytoplasm. There are a few areas of adipose tissue infiltration within the glandular substance. While for the most part the cells are fairly uniform in size and have regular oval nuclei, there are a great many hypertrophic nuclei scattered irregularly throughout and there are small foci in which the cytoplasm is greatly increased in amount without change in size of the nuclei. In such cells the cytoplasm has a uniform, fine pink granulation and no mitotic figures were seen. There is a distinct but thin capsule surrounding about half of the section and into this there is an irregular growth of glandular acini. There is, however, no evidence of malignancy. The tissue is typically that of the parathyroid gland, and the condition is one of hyperplasia of the glandular cells. Because of the localized character of the parathyroid enlargement, involving only one gland, the nature of the new growth may be regarded as neoplastic, that is, adenomatous in the sense of Castleman and Mallory.¹

Subsequent Course The patient stood the operation well and the first postoperative day was uneventful (May 30, 1935). On the morning of May 31, the second postoperative day, she developed a sensation of oppression in the chest, increased irritability, tingling in the fingers, and positive Chvostek and Trousseau signs. The serum calcium was 9.1 and phosphorus 2.2 milligrams per 100 c.c. For 10 days she had symptoms of tetany, which were easily controlled by the administration of 8 c.c. of 40 per cent calcium chloride four times a day and two doses of calcium gluconate intravenously on the third and fourth postoperative days. At no time was it found necessary to give Collip's parathyroid extract. By June 28, 1935, it seemed probable that she could not pass the stone in the left ureter and on that day it was removed by Dr. E. H. Barksdale.

The partial analysis of the stone was as follows: Weight of stone (oven-dry) 155.6 milligrams, $\text{Ca}_3(\text{PO}_4)_2$ 38.1 per cent, CaC_2O_4 (oxalate) 43.4 per cent, urates, trace, carbonate, trace, cystine, trace, percentage of stone as Ca, 28.3 per cent.

The patient's recovery was uneventful and she was able to leave the hospital on July 13, 1935, her only symptom was occasional mild tingling in the arms.

Re-admission The patient was readmitted to the hospital on September 9, 1935, for calcium metabolism studies. Her only complaints were edema of the ankles and symptoms suggestive of mild tetany. She had gained 23 pounds in weight and felt better than ever before. The physical examination revealed a cheerful, adult female. The skin was warm, dry, and there was a papular pruritic rash with an erythematous base over the ankles and the lower part of each leg. The spine and extremities were not tender. The neurological examination was negative.

At this time the laboratory data were as follows: Urine Specific gravity, 1.007, no albumin, sediment three to four white blood cells, no red blood cells. Blood Red blood cell count 4,000,000, white blood count 8,000, hemoglobin 12.2 gm. Venous

pressure in the arms was 85 millimeters of saline. Blood non-protein nitrogen 38 milligrams per 100 c.c. Serum protein 6.4 per cent, albumin 4.4 per cent and globulin 2.0 per cent. Serum calcium 9.8 milligrams per 100 c.c. Roentgen-rays showed little change in the cranial bones, but the wing of the left ilium showed bone structure much nearer normal than on any previous occasion.

The metabolic studies were repeated and are shown together with the preoperative studies in table 1. Compared with the preoperative period when the total calcium excretion for three days was 1,335 milligrams, of which 931 milligrams appeared in the urine and 424 milligrams in the feces, the total excretion now for three days was only 558 milligrams, of which 169 milligrams appeared in the urine, and 389 milligrams in the feces.

TABLE I

Calcium Excretion on Low Calcium Diet before and after Removal of Parathyroid Adenoma (three-day metabolism period, diet containing approximately 0.3 gm calcium per day)

5/15/35-5/17/35 (Before) Gm Calcium		9/15/35-9/17/35 (After) Gm Calcium	
Urine	Feces	Urine	Feces
0.931	0.425	0.169	0.389
Per cent excreted in urine 69%		30%	

The values of the preoperative and postoperative serum calcium and phosphorus determinations are represented in figure 2. Before operation, the serum calcium was high, ranging from 12.5 to 13.5 milligrams per 100 c.c. and the serum inorganic phosphorus was low, varying from 1.7 to 3 milligrams per 100 c.c. After recovery from the operation the serum calcium varied from 9.8 to 10.1 and the serum inorganic phosphorus from 3.0 to 4.7 milligrams. These findings indicate clearly that the hormone from the adenoma was directly concerned in the hypercalcemia which was present before the operation.

DISCUSSION

Von Recklinghausen² in 1891 first called attention to the condition known as *osteitis fibrosa cystica*. He emphasized the generalized nature of the disease, pointing out that it affected all the bones, thus differing from the solitary cysts of bone or benign giant cell tumors. In 1904, Askanazy³ first described a case of *osteitis fibrosa cystica* associated with a parathyroid adenoma. Erdheim⁴ in 1907 described three cases of osteomalacia associated with parathyroid tumors. In 1923 Dawson and Struthers⁵ pointed out the frequent association of renal calculi with the presence of areas of metastatic calcification in the lungs, kidneys, and myocardium in cases of *osteitis fibrosa cystica*. It was not until 1926, however, that Mandl⁶ performed the first operation for the removal of a parathyroid tumor in a case of *osteitis fibrosa cystica*. The patient completely recovered.

Collip⁷ in 1925 discovered parathormone and studied the effect of experimental hyperparathyroidism. He found that the essential characteristic was the development of hypercalcemia sometimes exceeding 20 milligrams per 100 c.c. of serum.

In 1930 Hannon Shorr, McClellan and DuBois⁸ studied the biochemical aspects of *osteitis fibrosa cystica* and through their investigations definitely established the presence of hypercalcemia and hypophosphatemia. In the same year Bauer, Albright and Aub⁹ described the increased urinary output of cal-

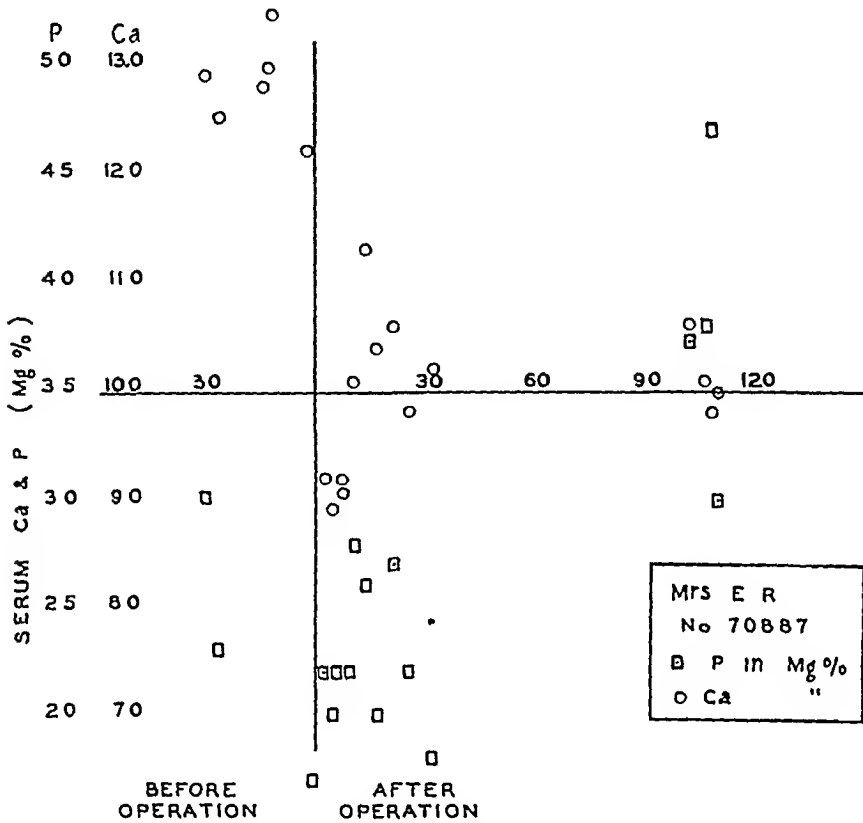


FIG 2 Calcium and phosphorus studies made before and after operation. The numbers on the longitudinal ("normal") line indicate days before or after operation. The day of operation is indicated by the vertical line.

cium and phosphorus in a case of *osteitis fibrosa cystica*. They found it to be six to seven times greater than in the normal individual. They also found that these changes in metabolism were equivalent to those of a normal individual receiving 100 units of parathyroid hormone daily. Excellent reviews of the subject of hyperparathyroidism have been published, notably by Hunter and Turnbull,¹⁰ Barr and Bulger,¹¹ and Jaffe.¹² Recently Castleman and Mallory¹ have studied the histology of the parathyroid glands in cases of hyperparathyroidism.

In 1934 Albright, Aub, and Bauer¹³ reported 17 proved cases of hyperparathyroidism. They gave a detailed description of the condition and described the following clinical types: (1) classic hyperparathyroidism (Von Recklinghausen's disease). Skeletal manifestations predominate and consist of decalcification, cysts, tumors, and eventually fractures. (2) Osteoporotic form of hyperparathyroidism. Presenting symptoms are due to general decalcification and there are no cysts or tumors. (3) Hyperparathyroidism with

nephrolithiasis Presenting symptoms are associated with renal stones and with no gross skeletal changes (4) Hyperparathyroidism with renal insufficiency (nephrocalcinosis) The symptoms are those of Bright's disease (5) Acute parathyroid poisoning This is a condition simulating acute parathyroid poisoning in dogs with sudden death and characteristic pathologic changes (6) Hyperparathyroidism simulating (or complicated by) Paget's disease In this classification our patient belongs to types 2 and 3, presenting renal symptoms extending over a period of 17 years, and finally, manifestations of generalized decalcification without cysts or tumors

COMMENTS

In view of the increase in the number of reported cases in recent years a resume of the important clinical features of hyperparathyroidism is given This disease may occur at any age period The youngest patient reported by Bauer, Albright and Aub was 13 years of age and the oldest 62 years of age, although most cases fall in the middle age group The sexes are equally affected

Although a positive diagnosis cannot be made without chemical data, the symptoms of hyperparathyroidism are usually quite characteristic The onset is insidious and may consist only of mild pains in the bones In the instances where the skeletal changes predominate, a spontaneous fracture may be the first event that calls attention to the disease In more advanced hyperparathyroidism muscular weakness, lassitude and hypotonia are constant symptoms and may finally lead to difficulty in coordination There is diminished irritability of muscle to electrical stimulation These symptoms are attributed to the hypercalcemia Many patients with the disease are classified and treated as neuroasthenics prior to the recognition of the true nature of their symptoms

Hyperparathyroidism with renal manifestations may present symptoms exclusively renal and these may have persisted for many years These are symptoms of renal calculus, pyelitis, pyelonephritis with or without gravel Increased thirst, which is attributed to the increased excretion of calcium and phosphorus, is commonly present Polyuria, however, is not always present and it is interesting to note that when it occurs the incidence of stones is less Bone symptoms may be vague or entirely absent Albright, Baird, Cope and Bloomberg¹⁴ in a study of the renal complications of hyperparathyroidism emphasize that all of the symptoms and signs of nephritis may be present They stress the importance of the recognition of the accompanying bone changes in the diagnosis of the underlying hyperparathyroid state in such cases They further point out that with profound kidney damage there is interference with calcium and phosphorus excretion in the urine Albright, Aub and Bauer¹³ report eight instances of hyperparathyroidism discovered as a result of performing routine blood calcium and phosphorus determinations in all patients with urinary calculi

Clinically, hyperparathyroidism may resemble other conditions as osteomalacia, solitary cysts, Paget's disease, senile osteoporosis, solitary benign giant cell tumor, osteogenesis imperfecta, multiple myeloma, metastatic malignancy, renal rickets and basophilic adenoma of the pituitary (Cushing's disease) An excellent discussion of the differential diagnosis is given by Albright, Aub and Bauer,¹³ by Jaffe,¹² and by Gutman Swenson and Parsons¹⁷

Hyperparathyroidism cannot be accurately diagnosed without the demonstration of the presence of biochemical disturbances which occur in the body as a result of the over-secretion of the parathyroid hormone. Of significance are high serum calcium and low serum phosphorus values in the blood. These values may vary from 12.5 milligrams to over 20 milligrams of calcium per 100 c.c. of serum, and from 1.0 to 3.0 milligrams per 100 c.c. of inorganic phosphorus. These metabolic changes are not in themselves diagnostic, for high calcium values may occasionally be observed in multiple myeloma, metastatic carcinoma of bone, and in certain diseases accompanied by hyperproteinemia. Moreover in not a few instances of hyperparathyroidism the inorganic phosphorus may be normal. The most convincing chemical evidence of hyperparathyroidism is the demonstration of alterations in the calcium balance controlled over a period of time on a fixed low calcium diet. A negative balance indicating an excretion of calcium in excess of that ingested strongly supports the diagnosis. Although calcium excretion in the feces varies with the intake, the urinary calcium nearly always maintains an abnormally high level in hyperparathyroidism. In certain instances, however, as in severe nephritis associated with renal insufficiency, the urinary excretion of calcium may be diminished and confuse the picture. In these cases the roentgen-ray evidence of generalized decalcification of bone will constitute a significant diagnostic finding.

Roentgen-ray findings, when they do exist, consist chiefly of deformities, cysts, tumors, fractures and evidence of generalized thinning of bone. This is best seen in the flat bones and in the skull. Occasionally irregular thickening may be observed in the temporal, parietal and frontal bones of the skull, but more commonly there is definite evidence of decalcification. In instances of renal involvement without bony changes, metastatic calcified areas in the kidneys may be present. The most important roentgen-ray finding, however, is a progressive thinning of all bones.

Treatment. The medical treatment of hyperparathyroidism is of no value. Diets high in calcium and phosphorus may prevent the decalcification of bone, but increase the incidence of renal calculi. It is generally agreed that vitamin D is of little value. The treatment is surgical and the surgeon may expect a good-sized tumor in cases with marked hyperparathyroidism. But he must be a good surgeon and courageous for one does not always find the tumor at the common site for the parathyroid glands. A search for the tumor may lead him into the anterior mediastinum. It must be borne in mind that removal of a normal parathyroid gland is dangerous and may lead to marked postoperative tetany which may be fatal. The surgeon must also exercise careful judgment in deciding upon how much to remove. For here, as in the thyroid, the decision between a sub-total removal and complete extirpation may affect the future of the patient's life. It must also be borne in mind that parathyroid tumors may be multiple and if the removal of one does not cure the patient a second operation may have to be performed at a later date.

The complication that arises after operation is postoperative tetany. Increased irritability of the muscles, carpo-pedal spasm, positive Chvostek and Trousseau signs may appear within the first 24 hours after the operation. They are accompanied by marked diminution of calcium in the urine and return of the serum calcium to normal or subnormal values. The low values may persist

for weeks and even months after the operation. The control of postoperative tetany is obtained by the administration of calcium by mouth, calcium gluconate intravenously and Collip's parathyroid extract. Calcium in some form must be administered frequently, as it is very rapidly excreted. Eventually a readjustment of the activity of the remaining parathyroid tissue occurs and these symptoms disappear.

The improvement following operation is dramatic. The patient's general appearance changes, lassitude is replaced by a feeling of energy and the bone pains immediately disappear. Changes in bone structure may be observed by repeated roentgenographic examinations. Although these changes do not parallel the marked symptomatic improvement the bones eventually present a normal appearance.

SUMMARY

A case record of adenoma of the parathyroid gland with hyperparathyroidism and renal calculus (calcium stone) is presented. The preoperative diagnosis was based on a history of renal colic for many years, the roentgenographic evidence of decalcification of bone, and the presence of a negative calcium balance with hypercalcemia, hypercalciuria and hypophosphatemia. An adenoma of the parathyroid gland was removed at operation. Prompt recovery from the hyperparathyroid state ensued.

Calcium metabolism studies made before and after operation are recorded.

BIBLIOGRAPHY

- 1 CASTLEMAN, B., and MALLORY, T. B. The pathology of the parathyroid gland in hyperparathyroidism, *Am. Jr. Path.*, 1935, **vi**, 1.
- 2 RECKLINGHAUSEN, F. VON. Die fibrose oder deformierende Osteitis, *Festschr. f. Rudolph Virchow*, Berlin 1891, 1-89.
- 3 ASKANAZY, M. Über Osteitis deformans ohne osteoides Gewebe, *Arb. a. d. Geb. d. path. Anat., Inst. zu Tübingen*, Leipzig, 1904, **iv**, 398.
- 4 ERDMANN, J. Über Epithelkörperbefunde bei Osteomalacie, *Sitzungsber. d. k. Akad. d. Wissensch.*, Wien, 1907, **cxvi**, 311.
- 5 DAWSON, J. W., and STRUTHFRS, J. W. Generalized osteitis fibrosa, *Edinburgh Med. Jr.*, 1923, **xxx**, 421-564.
- 6 MANDL, F. Therapeutischer Versuch bei einem Falle von Osteitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors, *Zentralbl. f. Chir.*, 1926, **liii**, 260-264.
- 7 COLLIP, J. B. The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium, *Jr. Biol. Chem.*, 1925, **lxiii**, 395-438.
- 8 HANNON, R. R., SHORR, E., McCLELLAN, W. S., and DuBois, E. F. A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the parathyroid bodies, metabolic study I, *Jr. Clin. Invest.*, 1930, **viii**, 215-227.
- 9 BAUER, W., ALBRIGHT, F., and AUB, J. C. A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the parathyroid bodies, metabolic study II, *Jr. Clin. Invest.*, 1930, **viii**, 229-248.
- 10 HUNTER, D., and TURNBULL, H. Hyperparathyroidism: generalized osteitis fibrosa, *Brit. Jr. Surg.*, 1931, **xix**, 203-284.
- 11 BARR, D. P., and BULGER, H. A. The clinical syndrome of hyperparathyroidism, *Am. Jr. Med. Sci.*, 1930, **clxxix**, 449-476.

- 12 JAFFE, H L Hyperparathyroidism (Recklinghausen's disease of bone), Arch Pathol, 1933, xvi, 63, Ibid, 1933, xvi, 237
- 13 ALBRIGHT, F, AUB, J C, and BAUER, W Hyperparathyroidism, Jr Am Med Assoc, 1934, cii, 1276-1286
- 14 ALBRIGHT, F, BAIRD, P C, COPE, O, and BLOOMBERG, E Studies on the physiology of the parathyroid glands IV Renal complications of hyperparathyroidism, Am Jr Med Sci, 1934, clxxxvii, 49-64
- 15 GUTMAN, A B, SWENSON, P C, and PARSONS, W B The differential diagnosis of hyperparathyroidism, Jr Am Med Assoc, 1934, ciii, 87-94

SUBACUTE BACTERIAL ENDOCARDITIS OF THE MITRAL VALVE PREVIOUSLY RENDERED INCOMPETENT BY INFARCTION OF THE PAPILLARY MUSCLE AND SHORTENING OF THE CHORDAE TENDINAE*

By I I LEMANN, M D, F A C P, *New Orleans, Louisiana*

THE present communication is made as a contribution to the study of two problems first, the production of murmurs in coronary infarction, and second, the pathogenesis of subacute bacterial endocarditis. The occurrence of murmurs and of subacute bacterial endocarditis in relation to coronary infarction have both been repeatedly reported. The significance which I wish to attribute to them in the light of the case to be reported is new.

CASE REPORT

Male, aged 53 (at the time of the attack), suffered a coronary infarction on January 2, 1931. The evidence was convincing. He had pain in his chest and numbness of his arms. The pain in his chest was over the sternum and precordium. The patient did not remain quiet, but was constantly moving about. The pain came on during the night and lasted several hours when he summoned me about 6 a m, January 2. At that time the blood pressure was 180/120 mm of Hg, the heart rate was 80, without any abnormalities of rhythm or sound, A₂ was accentuated. On January 3, the temperature rose to 101°, the pulse to 100, and the respiration to 30. The blood pressure was 175 systolic and 100 diastolic. On January 4, the temperature rose to 101°, the pulse was 100, respiration 20, and the blood pressure was 160/115 mm of Hg. On January 5, the temperature was 100.5°, the pulse 80, and the blood pressure was 135/100. On January 6, the blood pressure was 125/90, and there was a soft systolic murmur at the apex. On January 7, sternal pain recurred during the night, temperature 100.5°, blood pressure 120/90. By January 9, the murmur had changed from the soft character previously described to the "zing" of the Jew's-harp character. The temperature continued to rise to 99 to 99.4°. On January 10, the blood pressure was 90/65 mm of Hg, on January 11 it was 106/75, on January 12, 116/85, and on January 14, 130/95. There was then a systolic murmur at the second left interspace, but it was not musical there as it was at the apex. On January 16, the blood pressure was 116/90 and the heart rate 76, and on January 20, the blood pressure was 130/100. The electrocardiogram made on January 20 showed Auricular rate 80, ventricular rate 80, sinus rhythm. P-R interval, 0.16 sec, Q R S,

* Read by title at the Meeting of the Association of American Physicians, May 1935.
From the Department of Medicine, School of Medicine, Tulane University, and The Medical Service, Touro Infirmary.

0.09 sec Left axis deviation 1₂, inverted In the second lead the T take-off was high and the S-T interval above the iso-electric line Slurring of Q R S in all three leads

In April 1931, he had a slight elevation of temperature again to 101.5°, and with this some bloody sputum There were, however, no abnormalities found in the lungs on physical examination A roentgen-ray report on May 16, 1931 was as follows "Examination of Chest The right diaphragm is well within normal limits The left diaphragm is resting at a level somewhat higher than the right, which reverses the



FIG 1 Infarct of the intraventricular septum involving the papillary muscles of the posterior flap of the mitral valve Subacute bacterial endocarditis attacking the mitral valve

usual position However, the left diaphragm appears to be elevated by a large amount of gas contained in the stomach and colon beneath the diaphragm, probably elevating this The heart shadow measures 5 cm to the right, 11½ cm to the left, or a total of 16½ cm, while half the inside diameter of the chest measures 15½ cm The heart is therefore considered to be 1 cm larger than the standard for comparison The aorta is within normal limits The pulmonary fields show no visible evidence of pathologic change"

In November 1931, he again had some bloody sputum, but throughout 1931, until

the summer of 1932, he felt remarkably well and was quite active, even playing golf without fatigue. In August 1932, he had another febrile attack, with temperature rising to nearly 103° . He was sick nearly two weeks, during which time he again spat blood. The blood pressure had continued to range from 135 to 155 systolic, and from 100 to 110 diastolic. He had been made to lose considerable weight, 25 to 30 pounds, by restriction of intake of food, so that by June 1933 he weighed 143 to 145 stripped, less than he had weighed for 20 years. He had continued to play nine holes of golf without dyspnea or fatigue. This had been permitted in spite of great concern on my part. In December 1933, the blood pressure was 165/125. The electrocardiogram on January 9, 1933 was as follows: Auricular rate 103, ventricular rate 103, P-R interval, 0.17 sec., QRS, 0.10 sec., left axis deviation, slight shift down of S-T₁, slight slurring of R₁ and downward direction of R₂, low T₁₋₂, deep Q₁, P₂ diphasic. On June 9, 1934, the following note was made: "He has continued to play nine holes of golf three times a week. He is never out of breath, walks slowly and ascends stairs slowly. Has no longer any chest pains, only once in five months has he had these pains, and then at night. They passed off after he had eaten a few candies. He considers his heart better, it gives him much less concern. His nerves are in bad shape, in fact throughout the years he had been under very great nervous strain, and has had occasion for worrying a great deal. He has always slept restlessly and suffered much from insomnia, for which it was necessary for him to take amytal frequently."

Beginning on June 19, 1934, he was in bed for 18 days because of fever rising to 102° for which no cause could be found. After he was free of fever for 10 days he was allowed up again, but he never regained his strength, and during July he continued to complain of lassitude. On August 2, it was noted that he had temperature of 99.2° , and he was sent home again to bed. The temperature began to range then from normal in the morning to a maximum of 101° in the evening. No definite cause for the temperature was found until a blood culture, taken on August 11, showed *Streptococcus viridans*. The number of colonies increased rapidly, and on September 23, there were 250 colonies of *Streptococcus viridans* per cubic centimeter of blood. Repeated transfusions of whole blood, 250 c.c. each time, were given at intervals of a week from August 17 to October 18. Although the number of colonies diminished, so that on October 16 there were only two colonies per cubic centimeter of blood, the condition throughout September and October remained about the same except for a progressive loss of weight. There were never any petechiae. The second week in November he had great tenderness of the palms of both hands over the pads at the base of the phalanges, and also on the soles of the feet at the base of the phalanges. This tenderness lasted for a few days. Throughout September, October and November there was great soreness and stiffness of the neck muscles. The spleen was never felt, and there never was any indication of embolism in the spleen or elsewhere. The temperature range throughout September, October and November was low, usually to a maximum of 100.5° occasionally to 101° . On November 12, the temperature rose to 103° , and the next 10 days to his death on November 21 were quite stormy. On November 12, he had a coughing spell, becoming very hysterical. The next night there was a sudden edema of the lungs, and the patient was practically pulseless. The surface of the body was cold and clammy. He was apparently moribund on November 14, 15 and 16, but on November 17, he was better and even oriented at times. The temperature ranged up to 103° . On November 18, 19 and 20, he was in delirium and stupor, practically pulseless. On November 20 and 21, there was dullness throughout the right lung posteriorly with bronchovesicular breathing, and dullness and crepitant râles at the base of the left lung. He died on November 21. Respirations had gone to 60, the temperature to as high as 105° .

I am indebted to Drs. John A. Lanford, Samuel Colvin and Kurt Neugarten for the following notes on the autopsy.

Autopsy Report The body is that of a white male, apparently 50 years of age, approximately 5 feet 11 inches in length, and weighing about 150 pounds. The body shows some evidence of loss of weight, although the fat is still normally distributed. No petechiae are noted. The thorax is well developed and of the sthenic habitus. The abdomen is slightly distended. There are no scars. The left side of the scrotum reveals a left hydrocele measuring about 6 cm in diameter, and containing approximately 50 cc of light straw colored fluid. The extremities show no changes. The cervical and axillary lymph nodes are not enlarged but the inguinal nodes show slight adenopathy.

Peritoneal Cavity The peritoneum is smooth and glistening. There are about 500 cc of straw colored fluid present. The appendix is normal. The urinary bladder is not distended. The spleen is enlarged in size and in its usual location, as is the liver. The other abdominal viscera are in their normal positions. The diaphragm extends to the fifth rib on the right side and the fifth intercostal space on the left. The mesenteric lymph nodes are not enlarged. The stomach and intestines are greatly dilated.

Thoracic Cavity The parietal pleurae are smooth and glistening. There is no free fluid present and only a few recent fibrinous adhesions on the outer side of the lower lobe of the right lung. The right lung shows a large solid area involving almost entirely the lower middle and part of the upper lobes. The left lung shows only patches of pneumonia here and there. The heart is in its usual location but is greatly enlarged.

Heart and Pericardium The parietal pericardium is covered over nearly its whole extent with a light cheesy appearing material. About 20 cc of cloudy fluid containing many small flecks of fibrin are present. The fibrinous exudate is particularly abundant over the right auricle and the great vessels, less so over the left auricle and left ventricle. The heart is considerably larger than normal. It has lost the normal conical shape. There is a moderate amount of fat beneath the epicardium through which the muscle appears as brownish-red in color. Over the right ventricle and to a considerable extent over the posterior aspect of the left ventricle, this brownish-red muscle exhibits irregular areas varying in size shining through the epicardium as islands with a large grayish-yellow center and a pinkish-red periphery (areas of apparent necrosis). At the posterior sulcus longitudinalis there is a large dull ivory white area (3 by 5 cm). This involves chiefly the left ventricle but extends also for a small distance to the right ventricle. Palpation reveals this area to be thinner and less resistant than the rest of the ventricular wall, yet one has the impression that it is more solid—a thin fibrous scar.

The right auricle, somewhat increased in size, is partly occupied by an *ante mortem* thrombus (fibrinous mass) which completely fills up the auricular appendage and extends into the upper half of the auricle. Beneath this exudate the endocardium is partly ulcerated. The tricuspid and pulmonary valves are normal. The tricuspid orifice admits four finger tips. The foramen ovale is closed. The chamber of the right ventricle is also increased in size. Sections through its wall show irregularly scattered areas of necrosis similar to those already described as seen on the external surface of the heart.

The chamber of the left auricle is markedly dilated. The mitral orifice admits two finger tips. Here the endocardium is thick, grayish-white, and the muscle is not to be seen through it. There is an ulceration (3 by 2.5 cm) on the anterior left lateral wall of the chamber. This extends down on to the auricular surface of the mitral valve. On the endocardium above the line of attachment of the posterior mitral flap, there are flat, granular, grayish-pink vegetations with two tongue-like continuations upon the floating part of the valve. These "tongues" reach the free edges of the valve and present a picture resembling a horseshoe. Besides these vegetations on the

auricular aspect of the posterior flap, there are other similar ones toward the aortic flap of the mitral valve, chiefly where the two flaps are joined anteriorly. These vegetations vary from miliary to lentil size and consist of smooth grayish-white fibrinous verrucae upon which pinkish granular punctiform spots are seen here and there. These vegetations continue upon the ventricular aspect of the valve and also for almost 1 cm upon the chordae tendinae of the posterior flap of the valve.

The left ventricular chamber is somewhat ballooned out, this being particularly noted in the posterior part of the interventricular septum corresponding to the region of the fibrous scar previously described. The internal aspect of this area is grayish-red and differs distinctly from the surrounding brownish-red of the rest of the ventricular wall. The endocardium, however, is smooth. The upper corner of the oval shaped area of the scar forms a deep depression in the muscular wall. There, the trabeculae carneae have completely disappeared leaving only small flattened bridges at the base of the scar. Further, one notes a difference in the structure of the anterior and posterior ventricular wall (internal aspect) as well as of the papillary muscles. The anterior papillary muscle and the trabeculae carneae of the anterior wall have their normal shape. The posterior papillary muscle, the base of which is included in the scar, is shortened and appears as a flat strip merging into the ventricular wall. The tips of the papillary muscle can no longer be seen. The thin smooth chordae tendinae are stretched. They hold the posterior flap of the mitral valve down against the posterior wall of the ventricle so that during life only slight movement of this posterior flap could have been possible.

The attached portion of the aorta shows some slight thickening in the sinuses of Valsalva around the orifices of the coronary vessels. The right coronary when opened is found completely thrombosed. The left coronary is thickened and its lumen generally narrowed being represented by a mere pin-point opening. It is free from thrombus formation except in its smaller subdivisions. The aortic cusps are normally thin and smooth. The wall of the left ventricle measures 13 to 15 mm in thickness and on section has a mottled appearance. There are dirty yellow areas surrounded by a brownish-red ring.

Lungs The right lung measures 22 cm in length, 12 cm in width by 6 cm in thickness. The external surface shows a massive area of bluish-black discoloration extending over the entire surface with the exception of a small area along the periphery of the lower lobe and the upper half of the upper lobe. Along these latter areas are small patches of emphysematous tissue. The remainder of the lung is solid and of the consistency of liver, and on section is deep red in color and upon pressure only bloody material escapes, there being no air in this portion. A bloody frothy fluid escapes from the periphery. Weight 750 grams.

The left lung measures 22 cm in length, 11 cm in width by 5 cm in thickness. The external surface is pinkish-red in color and is streaked with areas of bluish-black scattered throughout both lobes. The cut surface is pinkish-red in color for the most part and upon pressure exudes a frothy blood-tinged fluid. There are some small consolidated areas throughout the parenchyma, several of which are somewhat triangular in shape. Weight 425 grams.

Liver The liver measures 20 cm in length, 26 cm in width by 7 cm in thickness. Its external surface is smooth and glistening, and brownish-red in color, mottled with many small areas of yellowish discoloration. Upon section, the organ is typically nutmeg in appearance and generally congested. Innumerable small yellowish-white specks stand out prominently. The organ is very much enlarged. Weight 1615 grams.

Gall-Bladder The gall-bladder is almost collapsed and contains only a small amount of bile. No stones are palpated. The external surface is adherent to the omentum and is torn away with much difficulty. It is pinkish-yellow in color, smooth and glistening except in the adherent areas.

Adrenals The adrenals are pyramidal in shape, measuring 4 to 3 cm. The external surface is slightly lobulated and pinkish-yellow in color. Upon section, the cortex is dirty yellow in color and not well differentiated from the medullary portion.

Kidneys The left kidney measures 12 cm. in length, 7 cm. in width by 5 cm. in thickness. There are several large retention cysts seen externally, extending into the kidney tissue for $1\frac{1}{2}$ cm. in depth. The external surface is lobulated and granular in appearance. The capsule strips with some difficulty revealing a granular pinkish-red congested surface. The cut surface reveals a cortex which is well differentiated and measures from 5 to 7 mm. in thickness. The organ is congested in appearance. There is a large amount of fat in the pelvis. Weight 190 grams.

The right kidney measures 12 cm. in length, 6 cm. in width by 5 cm. in thickness. It varies in no way from the left kidney with the exception that the retention cysts found here are much smaller than in the left kidney. Weight 175 grams.

Pancreas The pancreas measures 20 cm. in length, 4 cm. in width by $1\frac{1}{2}$ cm. in thickness. Its external surface is pinkish-yellow in color and lobulated in appearance. The cut surface is yellow in color and lobulated. The organ shows no gross changes with the exception that it is more flabby than usual. Weight 110 grams.

Spleen The spleen measures 15 cm. in length, 10 cm. in width by 5 cm. in thickness. Its external surface is grayish-red in color and smooth and glistening with the exception of two large raised infarcts which are present at the upper and lower poles respectively. These infarcts are pale pinkish-orange in color and are sharply demarcated from the surrounding tissue. Upon section they are $1\frac{1}{2}$ cm. and 1 cm. in diameter respectively, both exuding a purulent yellow discharge from their bases. The infarcts themselves are necrotic and friable. The remainder of the cut surface of the spleen is deep red and congested in appearance with innumerable small yellowish areas of focal necrosis seen scattered throughout the surface. Weight 300 grams.

Gastrointestinal Tract The stomach is greatly distended with air as are the entire small and large intestines, especially the cecum.

Blood culture, taken at autopsy under sterile precautions, shows the presence of *Streptococcus viridans*.

Anatomical Diagnoses Coronary thrombosis with infarction (old and recent), *Streptococcus viridans* septicemia, subacute bacterial endocarditis, mitral, acute and chronic myocarditis, ante-mortem thrombus of right auricle, pericarditis, fibrinous, lobal and lobular pneumonia, chronic nephritis, multiple infected infarcts of spleen, passive congestion of liver and spleen, hydrocele.

THE SIGNIFICANCE OF MURMURS OCCURRING IN CORONARY THROMBOSIS AND CARDIAC INFARCTION

Murmurs in cases of coronary thrombosis are mentioned by most writers. Paul White,¹ for example, writes "Murmurs may or may not occur, the commonest is that of functional mitral regurgitation due to dilatation—an apical systolic murmur—although at times a sclerotic change involving the base of the mitral valve may result in organic mitral regurgitation. Basal murmurs are less common in coronary disease, an aortic systolic murmur may be found, due to aortic dilatation, in turn usually resulting from an associated hypertension, but sometimes such a murmur is due to aortic stenosis caused by sclerotic involvement of the aortic valve, if this latter process is marked a systolic thrill will be felt over the aortic area and will be transmitted into the neck. An aortic diastolic murmur is much less common but may result from either of the lesions just noted which produce the aortic systolic murmur." Samuel Levine² writes "In almost half of the cases a slight or moderately loud systolic murmur can be heard,

and very rarely an aortic diastolic murmur. This latter finding was present in only one case of this entire series, and he had aortic stenosis and insufficiency. There was not a single instance of mitral stenosis in this group. In about one-half of the cases no murmur whatever could be heard." Castex^{3,4} has described in cases of cardiac infarction murmurs heard during part of systole (telesystolic in contradistinction to holosystolic, heard throughout systole). Castex claims priority in having related merosystolic souffles to infarct of the myocardium. In his first article he attempts to explain the pathogenesis of the souffle as follows: "According to these findings it is logical to admit that the merosystolic souffle originates by vibration of the blood column upon contraction of the infundibular region of the left ventricle, due to the fact that the blood column finds itself in zones of different dimensions as a result of the infarct which placed a zone of that region in such a manner as to make contractions impossible. This theory explains the merosystolic souffle in the two patients and in turn is firmly based on it." In his second communication Castex refers to the experiments of Bondi who "arrived at the conclusion that most if not all of the cardiac souffles were the result of the vortex action of the blood column."

"According to the conception of Bondi there exists not merely one source for the souffles but there are many locations where the souffles may be produced. They may be distributed over the greater part of the internal ventricular wall. These locations are particularly numerous in the apex region of the ventricular cone." DiCio and Battio⁵ report a case of painless coronary occlusion in which the diagnosis was based chiefly on the finding of a merosystolic (meso- and telesystolic) souffle. The diagnosis was confirmed at autopsy. Hyman and Parsonnet⁶ write "About one half of the patients suffering from acute coronary thrombosis exhibit cardiac murmurs. These murmurs are usually systolic in time but occasionally a diastolic blow may be heard at the base of the heart. The mechanism responsible for the establishment of these murmurs apparently is concerned with the dilatation phenomena of the heart muscle encompassing the valvular orifices. For this reason the murmurs will vary not only in their intensities but also in their duration and time factors. Indeed, it is not uncommon to observe many alterations in these three characteristics throughout but a single day." "We have not been able to draw any definite conclusions in regard to prognostic information to be derived from a close study of the murmurs developing for the first time during a coronary attack. At the same time, when such murmurs are discovered and when these show characteristic alterations at each succeeding examination, certain information may be secured in regard to the state of the heart muscle. Of all the various phenomena developed by the coronary thrombosis syndrome murmurs are unquestionably of the least importance." It will be noted that after the murmur in my case changed from a soft blowing character to one with the "zwing" of the jew's-harp there was no further change.

Dr. Fred Smith⁷ says "The damage to the papillary muscles and the mitral valve structures is an important feature in the sclerosis of the coronary arteries. The papillary muscles are likely to be involved by the occlusion of either of the main branches of the left coronary artery. The changes in these structures contribute to the alteration in the first heart sound at the apex and to the production of the systolic murmur frequently heard in this location." It occurred to

me, in considering the sequence of events in my case, that a reasonable explanation would be the location of an infarction at that point in the ventricular wall which would involve the papillary muscle, and I pictured to myself that an infarction at this point with resultant necrosis and connective tissue replacement must necessarily result in shortening of the chordae tendinae and limiting the closure of the mitral valve. We would thus have a mitral regurgitation due to organic disease though not of the mitral valve itself. This mental picture and *intra vitam* diagnosis of infarction involving the papillary muscles of the mitral valve was proved at autopsy to be correct.

SUBACUTE BACTERIAL ENDOCARDITIS COMPLICATING CORONARY INFARCTION

White¹ lists subacute bacterial endocarditis among the complications of coronary disease. "In addition to such complications as coronary thrombosis, cardiac aneurysm, cardiac rupture, congestive failure, heart-block, and other arrhythmias, and embolism from intracardiac thrombosis, coronary disease is frequently accompanied by hyperpiesia and general arteriosclerosis, sometimes by chronic rheumatic valvular disease, diabetes, nephritis, and cerebral hemorrhage or thrombosis, and less often by luetic aortitis, thyroid disease (either thyrotoxicosis or hyperthyroidism), bacterial endocarditis, and congenital defects." The sequence in which the relationship of the two conditions is usually thought of is embolism of the coronary artery due to subacute bacterial endocarditis. It is believed that the present report is the first of an implantation of subacute bacterial endocarditis upon a heart previously damaged by infarction. It is chiefly held that subacute bacterial endocarditis occurs only in hearts in which the valves are already abnormal by reason either of a congenital anomaly or of previous inflammatory disease. In the present case the mitral valve attacked by subacute bacterial endocarditis was neither anomalous, nor had it been the site of a previous inflammatory process. Apparently, therefore, a perfectly smooth and normal valve, when handicapped by congenital anomaly or by abnormal attachment (as for example shortening of the chordae tendinae due to infarction), falls easy victim to subacute bacterial endocarditis.

I wish to point out, too, the difference between my case and those reported by C Magarinos Torres² who divides his cases of parietal endocarditis into two large groups. In one of these groups parietal endocarditis is associated with valvular disease. This is what he calls valvulo-parietal endocarditis. In the other group the parietal endocarditis occurs with intact valves. This he terms genuine parietal endocarditis. In the case reported here subacute bacterial endocarditis attacked the smooth but handicapped mitral valve.

SUMMARY

1 A case of coronary thrombosis is reported in which on the basis of a systolic murmur a diagnosis of infarction involving the papillary muscle was made. This diagnosis was substantiated at autopsy.

2 It is suggested that the occurrence of murmurs may be used as an additional means of locating the exact point of infarction on the ventricular wall.

3 The handicapped mitral valve, though free of any previous inflammatory disease and of congenital anomaly, later became the site of subacute bacterial endocarditis.

REFERENCES

- 1 WHITE, P Heart disease, 1931, MacMillan Co, New York, p 420 and p 423
- 2 LEVINE, S Coronary thrombosis its various clinical features, *Medicine*, 1929, viii, 266
- 3 CASTEL, M R Merosystolic souffles, *Prenza med Argent*, 1931, xviii, 781
- 4 CASTEL, M R Souffles of the heart, *Prenza med Argent*, 1932, xix, 1153
- 5 DiCio, A, and BATTRO, A Value of the merosystolic souffle in the diagnosis of infarct of the myocardium, *Prenza med Argent*, 1933, xx, 150
- 6 HYMAN, A S, and PARSONNET, A E The failing heart of middle age, 1932, F A Davis Co, Philadelphia, p 175
- 7 SMITH, F M Diseases of the heart, in MUSSER's Internal Medicine (Chapter XI), 2 Ed, 1934, Lea and Febiger, Philadelphia, p 377
- 8 TORRES, C M On thrombosis of heart and mural endocarditis of non-valvular origin, *Mem d Instit Oswaldo Cruz*, 1928, xxi, 268

DIABETES REFRACTORY TO INSULIN, WITH REPORT OF A CASE

By SAMUEL S ALTSHULER M D F A C P and S E GOULD M D,
Eloise, Michigan

IN reviewing the literature on this subject one is struck by the fact that many cases are spoken of as "insulin refractory" which might better be termed "insulin resistant," that is, cases in which an unusually large amount of insulin must be administered in order to control the glycosuria. The case which we are reporting is truly insulin refractory, no relationship is demonstrable between the amounts of insulin given and the subsequent glycosuria.

In most instances the physiological responses to insulin are predictable, but the mechanism of its action is still problematical. The proper understanding of this mechanism is reserved for some time in the future when the etiology of diabetes mellitus shall be clear.

The theory that diabetes is the result of a functional disorder of the pancreas is based on the work of two groups. In 1889 Von Mering and Minkowski¹ showed that extirpation of the pancreas produces diabetes. In 1922 Banting and Best² in McLeod's laboratory demonstrated that diabetes may be controlled by the injection of insulin which is derived from the extracts of pancreatic islands.

Pathologically, typical and constant lesions characteristic of diabetes have never been found. The changes noticeable in the diabetic pancreas may also be present in the non-diabetic pancreas. Even in fatal cases of diabetes, where no pancreatic lesions are found, extraction of the gland shows the presence of insulin sufficient to continue life for several weeks. This fact and others have been advanced as evidence that one or more of the other organs in the body must have a part in the production of diabetes. The glycosuria may be due to secondary functional changes in the pancreas, or the action of the pancreas-produced insulin may be nullified by some other substance produced elsewhere in the body.

Although the hyperfunction of the thyroid has been said to impair the func-

* Received for publication August 26, 1935

From the Departments of Medicine and Pathology of the William J. Seymour Hospital, Eloise, Michigan, and the Department of Pathology of Wayne University, College of Medicine, Detroit

tional ability of the islands of Langerhans, clinically we have seen hypothyroidism co-exist with diabetes. The hypersecretion of the adrenal medulla has also been mentioned as a possible cause of diabetes, but Houssay and Lewis³ showed that diabetes in animals follows its usual course in the absence of the adrenal medulla.

There is far more evidence to involve the pituitary than either of the mentioned organs. Colwell⁴ has written a splendid review of the literature upon the relation of the hypophysis to carbohydrate metabolism, and Collip⁵ more recently has pointed out the experimental, chemical, and clinical evidence for the presence of a diabetogenic factor originating in the pituitary gland. The mutually antagonistic actions of pituitary extract and insulin have been well demonstrated.

In the treatment of diabetes, when the insulin requirement exceeds the anticipated amount, we must consider the presence of a complicating condition. Pollack⁶ has given a very good summary of the possibilities. Cases completely refractory to insulin, however, are not common and there are only three reported in the literature with autopsy findings. Two of these cases had pituitary tumors, the third, other diagnosable complications. Acromegaly in which there is an acidophilic adenoma of the pituitary is frequently associated with glycosuria.

Of the three cases mentioned, Mahler and Pasterny⁷ report one showing inactivity of insulin in an acromegalic with glycosuria. A tumor of the hypophysis was found at autopsy.

Ulrich⁸ reports a patient with a pituitary adenoma who had two attacks of pronounced glycosuria with hyperglycemia. The first period extended over a month and disappeared spontaneously. The second occurred two years later and continued until the death of the patient. Insulin had little effect on the level of the blood sugar during both of these periods.

The third case reported by Chailton,⁹ was complicated by pulmonary tuberculosis and luetic infection. The diabetes was relieved by anti-luetic treatment and the patient died of the tuberculosis.

The following case is reported because we feel that it helps to establish the relationship of the pituitary to carbohydrate metabolism.

CASE REPORT

Mrs. M. S., colored female, aged 35, was admitted to the William J. Seymour Hospital on August 9, 1933, complaining of blindness, headaches, and "diabetes."

The patient's "diabetes" was discovered incidentally at the Henry Ford Hospital in August 1928, when she was admitted for a laceration of the dorsum of the left hand and division of the tendons of the extensor digitorum communis and extensor pollicis. The laceration was repaired, the patient was placed under a diabetic regime, and insulin was prescribed, evidently she did not follow the diabetic treatment as she did not return after the laceration was healed.

She was next seen in the Out-Patient Clinic at the Detroit Receiving Hospital on August 25, 1931, complaining of headache and blurring of vision. Examination showed a markedly decreased acuity of vision in the right eye with light perception only in the left eye. Examination of the fundi was negative. She was seen about once a month, and after one year the vision in the right eye was also reduced to light perception only.

The etiology of the amblyopia was not determined. The patient's blood Wassermann and Kahn were negative, and roentgen-rays of the skull in 1931 and again in 1932 showed no signs of an intracranial lesion. Examinations of the fundi remained

negative. She was treated with diet and insulin but her diabetes was never controlled.

The patient said that during this time she had symptoms of polydipsia, polyuria and itching around the genitalia.

At the time of her admission to the Seymour Hospital, the patient had only light perception and was complaining of frequent distressing headaches.

In her catamenia, menses began at 13 years and were of the regular 28-4 day type. Her last menstrual period occurred two years before. Her husband and two children, 11 and 9, were all living and well.

The examination revealed a well-developed, well-nourished young colored female with constant grimacing of the face and rolling of the eyes. Both pupils were widely dilated and showed no reaction to light or accommodation, there was no evidence of cataracts. The fundus examination showed both discs to be well defined and pale although they did not appear atrophic. The arteries were small, with very little evidence of arteriosclerosis. There were no exudates or hemorrhages. The thyroid was not enlarged. The lungs were clear. The heart was normal and the blood pressure 110 mm of mercury systolic and 70 diastolic. The abdominal examination was negative. There was no edema of the extremities. The tendon reflexes were not obtained. The neurological examination was otherwise negative.

The laboratory examinations showed. Urine, slightly cloudy and acid with a specific gravity of 1.008 to 1.025, albumin, trace, sugar, + + + +, sediment (not catheterized), many white blood cells.

Blood count (August 10, 1933) hemoglobin, 12.9 grams, red blood cells, 4,500,000, white blood cells, 4,150, polynuclear neutrophils, 37 per cent, lymphocytes, 62 per cent, monocytes, 1 per cent. Blood calcium, 9.5 mg per cent. Blood Kahn, negative.

Spinal fluid (Dec 20, 1933) Kahn + + + +. Anti-luetic treatment in the form of iodides and bismuth was given and the spinal fluid test repeated on April 4, 1934, showing 6 cells, globulin, trace, sugar, 65 mg per 100 cc, colloidal gold curve 1111221000, Kahn negative.

The glucose tolerance test on January 3, 1934 showed fasting blood, 286 mg per cent, first hour 435, second hour 370, and third hour 350 with sugar in the urine in every specimen.

Roentgen-ray of the skull on December 9, 1933 revealed "Sella within normal limits. No evidence of erosion. No evidence of increased intracranial pressure."

The patient was placed on a diabetic diet containing carbohydrate 100 gm, protein 70 gm, fat 150 gm. An attempt was made to adjust the insulin as shown in figure 1, gradually increasing it to 85 units daily divided into four doses. This, however, did not desugarize the patient, and her blood sugar ranged between 250 mg and 322 mg per 100 cc. After 13 weeks with no success whatever in controlling the diabetes, the insulin was discontinued for two weeks, during which period the urine showed a constant glycosuria and became positive for acetone and diacetic acid and the blood sugar ranged between 272 mg and 344 mg per 100 cc. The total absence of insulin made no difference in the diabetic state except for the development of a ketosis.

Insulin was started again and given every four hours throughout the 24, totaling 120 units daily for one week. There was still a glycosuria and the blood sugar ranged from 192 mg to 286 mg per 100 cc. Because the patient objected to such frequent insulin injections, we administered 110 units daily in four doses for six weeks. The urine showed a glycosuria and the blood sugar ranged from 235 mg to 286 mg per 100 cc. The insulin was discontinued again for two weeks during which time the urine again showed positive acetone and diacetic acid with the glycosuria. The blood sugar ranged from 323 mg to 333 mg per 100 cc. Insulin was resumed in three daily doses totaling 96 units. This was continued for four weeks during which time the acetone and diacetic acid disappeared and glycosuria persisted with the blood sugar ranging from 216 mg to 392 mg per 100 cc.

During this entire period the patient complained of frequent severe headaches. Because of the lack of choking of the discs or evidence of increased intracranial pressure, it was deemed advisable to investigate the head somewhat further. An encephalogram was therefore done on April 21, 1934 by Dr. F. Schreiber. The roentgen-ray showed "No evidence of disturbance of the symmetry of the air-filled ventricular system."

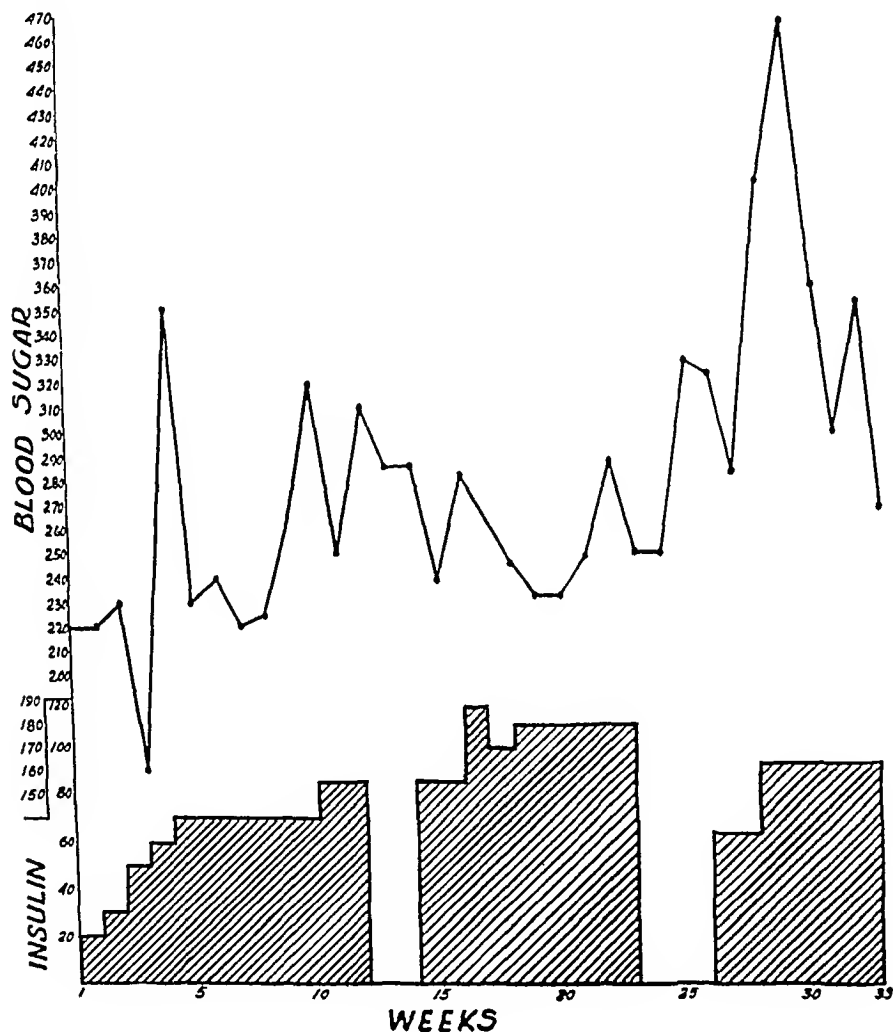


FIG 1

Following the performance of the encephalogram the patient vomited frequently and complained of severe headaches. Two days later she became unconscious and died on April 23, 1934. There were no clinical evidences of diabetic coma. The urine showed a one plus acetone. Blood sugar before death was 450 mg per 100 c.c.

PATHOLOGICAL REPORT

External Appearance The body is that of a well developed and nourished, obese, middle-aged, colored female, 165 cm in length. The hair is black and thick. The eyes and teeth are negative. The breasts are well developed and firm. The chest is

well developed. The abdomen is moderately distended with gas. The extremities and external genitalia are negative.

Cranial Cavity The meningeal vessels are congested. On lifting up the frontal lobes of the brain a circumscribed oval tumor, measuring 5 cm in length, 3 cm in width and 3 cm in depth is seen resting upon and adherent to the pituitary gland,



FIG 2 Sagittal view. Note cystic structure with fibrous wall, old blood content. Hypophysis attached below.

apparently attached to the stalk and posterior lobe. The tumor lies in relation to the following structures, all of which are compressed by it: the optic chiasm superior-anteriorly, the corpus callosum superiorly, and the cerebral peduncles and pons posteriorly. The arteries of the Circle of Willis are in close apposition to the tumor. Careful examination does not reveal origin of the tumor from any of the regional vessels. Upon sagittal section the tumor is seen to be free above and adherent to the pituitary below. It is cystic in nature, being distended by a dark, brownish-red, sanguineous fluid which is under moderate pressure. The walls of the cyst vary from 0.5 to 3.0 mm in thickness, are tough and fibrous, and in some places contain bits of lime. After escape of the fluid content a soft friable, almost crumbly dark brownish-red substance is seen. This arises from the inner lining of the cyst, over an area 1.5 cm in diameter. The remainder of the inner lining is quite smooth, and contains a number of scattered pinpoint sized spots of a shining colorless material, which upon examination under the microscope are seen to contain cholesterol crystals. The pituitary gland is compressed and flattened. The sella turcica is definitely deepened and ballooned beyond normal limits. The brain weighs 1150 gm.

Thoracic Cavity Both lungs are free from adhesions. The left lung weighs 400 gm and shows a smooth pleural surface. There is superficial congestion and edema. The cut surface is deep red in color and on pressing exudes a foamy sanguineous fluid. The bronchi are injected and the pulmonary vessels congested. The right lung weighs 400 gm and shows similar changes. The heart is soft and small, weighing 250 gm. The myocardium is congested and flabby. The left ventricle wall

measures 10 to 12 mm in thickness, the right ventricle wall 3 to 4 mm. The valves are negative. The coronary vessels and aortic arch are negative. The trachea and larger bronchi are injected. The thoracic and abdominal portions of the aorta are negative.



FIG. 3. Suprasellar hematoma with fibrous cyst wall compressing hypophysis.

Abdominal Cavity. The panniculus measures 5 to 6 mm. The entire bowel is distended with gas. The spleen weighs 125 grams. The capsule is grayish-blue in color and smooth. The parenchyma is soft and congested. The adrenals are of normal appearance. The kidneys each weigh 125 gm. The capsule of the left kidney strips easily exposing a smooth external surface. The cut surfaces are congested, the parenchyma very soft. The right kidney shows similar changes. The bladder, uterus, oviducts and ovaries are negative. The liver weighs 1200 gm. Externally it is smooth. The cut surface is pale brown and shows dilated central veins and irregular areas of fatty infiltration. The gall-bladder is distended with bile. The biliary tract and ampulla of Vater are negative. The esophagus, stomach, duodenum and small and large intestines are congested. The pancreas is normal in appearance.

Gross Diagnosis Suprasellar cyst (Craniopharyngioma?) Parenchymatous degeneration of heart liver and kidneys Generalized passive congestion Moderate intestinal distention

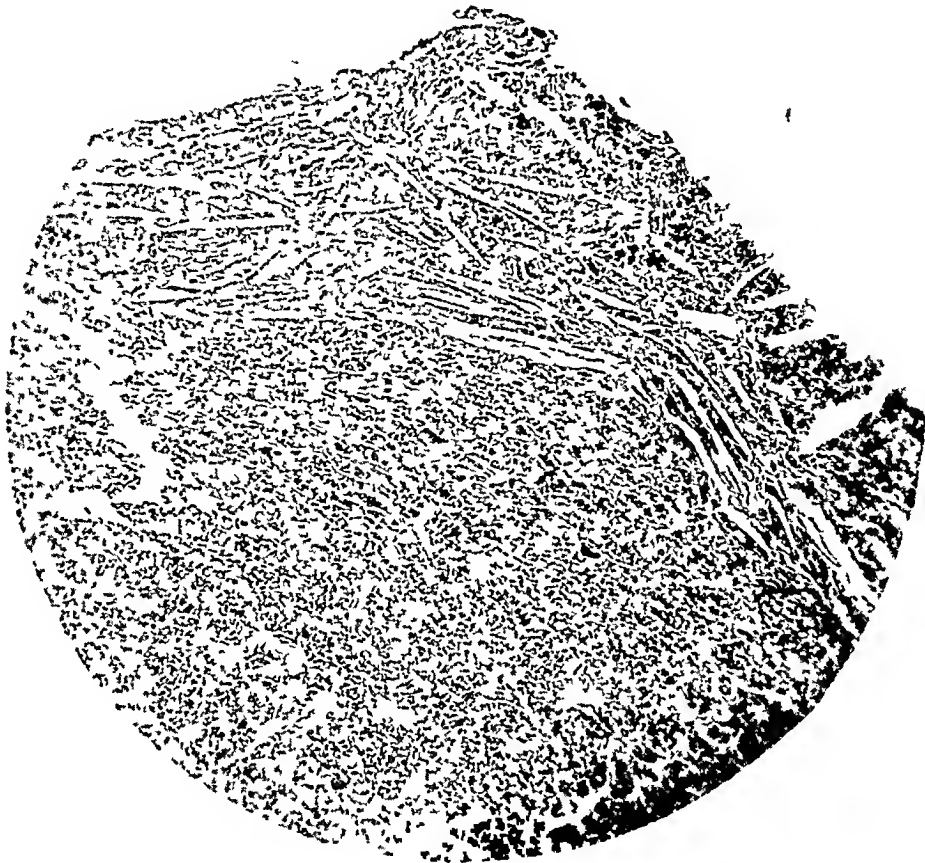


FIG 4 Wall of hematoma showing cholesterin clefts and compressed hypophysis

Cause of death sudden increase of intracranial pressure resulting in compression of circulatory and respiratory centers by the tumor mass

MICROSCOPIC EXAMINATION

The soft, friable, dark brownish-red substance within the cyst is made up of old blood and fibrin with a few scattered degenerating cells and contains a number of large cholesterin clefts. At the base of attachment to the cyst wall, this blood takes a brighter red stain. The cyst wall is made up of fibrous tissue which shows areas of fibroblastic proliferation on the inner surface, and a few areas of calcification. There are a number of regions on the inner surface showing foreign body reaction and focal accumulations of chronic inflammatory cells, consisting mainly of lymphocytes. One-fourth to one-half of the thickness of the cyst wall is made up of a

layer of epithelial cells of the anterior lobe of the hypophysis. This layer of cells lies toward the peripheral surface of the cyst wall, and consists mainly of chromophobic cells and acidophilic cells, among which the latter are prominent. Numerous chromophobic cells are seen to be undergoing degeneration, the cytoplasm having a ground glass appearance, and the nucleus being pale staining or absent. Many of the cells are disintegrating, while the outlines of others may still be recognized. In some areas groups of degenerating chromophobic cells have a foamy appearance. Due to degeneration of these cellular elements, the stroma is rendered prominent. Within the stroma, as within the fibrous tissue of the remainder of the cyst wall, there are a number of deposits of blood pigment.

The inner surface of the cyst shows no epithelial lining, and no suggestions of enamel or keratin materials.

These sections were reviewed by Dr. Carl V. Weller, Professor of Pathology, University of Michigan, whose interpretation follows: "In my opinion this is not a neoplasm. Neither is it a developmental cyst. The cystic structure here is essentially an old hematoma with a marked deposition of cholesterol and a foreign body giant-cell reaction about the cholesterol crystals. The nests of cells in the surrounding connective tissue are compressed cells from the anterior lobe and pars intermedia of the pituitary. This might well have been an aneurysm of the internal carotid artery or of the cavernous sinus or some other vascular structure, or an old hemorrhage."

SUMMARY AND COMMENT

This patient presents an example of diabetes entirely refractory to insulin. During the 34 weeks she was under observation the hyperglycemia and glycosuria had no relation to the amount of insulin administered. The total omission of insulin, however, resulted in a ketosis. This failure of insulin action suggests that the diabetes was not due to a dearth of insulin but that there was some factor present which had an inhibitory or antagonistic effect on both the endogenous and the exogenous insulin. At autopsy a large suprasellar cystic hematoma was found compressing the hypothalamic structure, including the anterior and posterior lobes of the hypophysis. This pathological finding points to the pituitary as the source of the antagonistic substance.

Whether this antagonistic effect is a direct one acting through the blood or on the tissue cells or on the liver is a matter for speculation and investigation. In this case no abnormal adrenal or thyroid factors were present either clinically or pathologically to suggest that the pituitary effect had come indirectly through these glands.

We are led to agree with Ulrich that the failure of insulin to produce its expected result in cases of glycosuria warrants consideration of the presence of a hypophyseal disturbance. The refractoriness to insulin may thus be considered as a diagnostic sign of the presence of a lesion in this region.

BIBLIOGRAPHY

- 1 VON MERING and MINKOWSKI. *Arch. f. exper. Path. u. Pharmacol.*, 1889, xxvi, 371.
- 2 BANTING, F. G., and BEST, C. H. *Internal secretion of pancreas*, Jr. *Lab. and Clin. Med.*, 1922, vii, 251-266.
- 3 HOUSSAY, A. B., and LEWIS, J. T. *Suprarenals and pancreatic diabetes*, *Rev. Asoc. med. argent.* 1921, xxiv, 1099-1103.

- 4 COLWELL, A R Relation of hypophysis to diabetes mellitus, *Medicine*, 1927, vi, 1-39
- 5 COLLIP, J B Diabetogenic, thyrotropic, adrenotropic and parathyrotropic factors of the pituitary, *Jr Am Med Assoc*, 1935, civ, 827
- 6 POLIACK H Insulin resistance, *Proc Staff Meet Mayo Clinic*, 1933, viii, 453
- 7 MAHLER, P, and PASTERNY, K Klinische Beobachtungen uber Insulin Wirkung beim Diabetes mellitus, *Med Klin*, 1924, xx, 337
- 8 ULRICH, H Antagonism between insulin and pituitary extract, *Arch Int Med*, 1928, vi, 855
- 9 CHARLTON, F H Diabetes refractory to insulin relieved by antidiabetic treatment, *Endocrinology*, 1924, viii, 235

EDITORIAL

SURGEON GENERAL CUMMING RETIRES FROM ACTIVE DUTY

THE retirement, on February 1, of Dr Hugh S Cumming, the fifth Surgeon General of the U S Public Health Service, marks the active conclusion of the distinguished career of an eminent sanitarian and public health leader Following his graduation from the University of Virginia in 1893, Dr Cumming entered the career corps of the Public Health Service (then called Marine Hospital Service) in 1894

His early work consisted of a variety of assignments, including epidemic duty during yellow fever outbreaks and outbreaks of smallpox He served at important maritime quarantine stations during the height of several yellow fever epidemics, and later served a tour of duty in the Orient Subsequently he was placed in charge of studies of Stream Pollution Investigations with which he was occupied for a period of several years

When Dr Cumming was appointed Surgeon General of the Public Health Service in 1920, he entered that important office with a background of experience that was most valuable in meeting the many perplexing problems that confronted him During the sixteen years that he served as Surgeon General of the Public Health Service he gave to that organization, as well as to the public health profession of the United States, an able leadership

Several important and outstanding achievements mark the four terms that Dr Cumming served as Surgeon General Among these may be mentioned the following

(1) The reorganization of the hospital work and expansion of the hospital facilities of the Public Health Service to meet the emergency of temporarily caring for ex-service men and women who were beneficiaries of the Veterans Administration

(2) The completion of the National maritime quarantine system by securing transfer to Federal control of the last State-owned quarantine stations in operation, which were located at the port of New York and at several ports in the State of Texas

(3) The establishment of a National Leprosarium for the care of lepers in the United States

(4) The successful control of outbreaks of bubonic plague at several ports

(5) The development and expansion of important research in field investigative activities of the Public Health Service

(6) The improvement and development of international relations and cooperation in public health affairs

Dr Cumming had the unusual distinction of serving as Surgeon General under five presidents

The Public Health Service is one of the oldest medical establishments in the Federal Government. Its origin dates from an Act of Congress approved by President John Adams on July 16, 1798. Until 1870 the principal functions of the Service were hospital care for American merchant seamen, and this work was conducted by the Treasury Department through local physicians. The first Surgeon General, Dr. John M. Woodworth, took office in 1871, and served for a period of eight years. He was succeeded by Dr. John B. Hamilton, who served for a period of twelve years. The third Surgeon General was Dr. Walter Wyman, who administered the work of the Service for a period of twenty years. Dr. Rupert Blue next served as Surgeon General for a period of eight years. Dr. Cumming, the fifth Surgeon General of the Public Health Service, served for sixteen years as administrative head of his organization.

Dr. Cumming became a Fellow of the American College of Physicians in 1923. His official duties interfered with his active participation in the annual meetings but he showed at all times a deep interest in the College. On the occasion of the Clinical Sessions in Baltimore he was instrumental in arranging as a special feature a day in Washington which included a most interesting program by members of the United States Public Health Service. Dr. Cumming was a member of the Board of Governors of the College for many years and was responsible for the proposal of a number of the officers of the Public Health Service for membership.

The medical profession and all persons interested in public health work view with extreme satisfaction the work accomplished by Dr. Cumming while serving as the head of the Public Health Service and the leader of the public health profession in this country. His ability and achievements were recognized not only throughout the United States but abroad, as he served as a member of the Health Section of the League of Nations, a member of the Permanent Committee of the International Office of Public Health, Paris, and as Director of the Pan American Sanitary Bureau. In his retirement from active service, the congratulations and best wishes of the medical profession attend him.

REVIEWS

Clinical Laboratory Methods By PAULINE S. DIMMITT, Ph G 156 pages, 15 × 22 cm F. A. Davis Company, Philadelphia 1934 Price, \$2.00

This small book presents very concisely the most used methods of clinical pathology, bacteriology, and blood chemistry. It is composed of 148 pages, and the author has divided it into 18 chapters. The methods described are those in common use, most of them having been subjected to long and critical tests. The tests are described in simplified terms, and it has the added advantages of illustrations. The book should be of the greatest value to those who wish to perform some of the most frequently used laboratory methods which are described by the author.

J. H.

Gynecology By BROOKE M. ANSPACH, M.D. Fifth Edition 832 pages, 19 × 26.5 cm J. B. Lippincott Company, Philadelphia 1934 Price, \$9.00

The fifth edition of Anspach's textbook of Gynecology is an excellent single volume work, meeting the needs of the teacher, student and practitioner. This edition is radically changed, for in order to include many of the newer ideas in regard to endometriosis, uterine bleeding, endocrine disturbances, etc., the text had to be altered and many sections re-written.

The plan of presentation follows, in a general way, that laid down in the earlier editions. The opening chapters deal with embryology, anatomy and physiology of the generative organs, and are followed by a section devoted to examinations of the genito-urinary organs and the lower intestinal tract. The following twelve chapters are devoted to a discussion of the injuries of the pelvic floor, malpositions of the uterus and the diseases of the external and internal generative organs, all being presented in a thorough and comprehensive manner. The chapters on ectopic pregnancy and ovarian tumor are of special interest. In addition to the affections of the generative organs, disorders of the urinary and intestinal tract are next taken up, their presentation being brief but adequate. The remaining sections are devoted to a discussion of various subjects, including backache, sterility, endocrine and menstrual disorders, irradiation therapy, pre- and post-operative preparation of the patient.

This treatise on gynecology is a practical work, clearly and concisely presented, based on the mature personal experiences of the author and on the knowledge obtained from the outstanding literary contributions of the world. The numerous illustrations, some being in color, are well selected and executed, adding greatly to the elucidation of the text. A sufficiently complete bibliography is found at the end of each chapter, which will be of aid to those desirous of more detailed information on the subject.

This work should prove of marked value to the student and practitioner, and is highly recommended.

J. M. H., JR.

Benjamin Rush, Physician and Citizen By NATHAN G. GOODMAN 421 pages, 16 × 23.5 cm University of Pennsylvania Press, Philadelphia 1934 Price, \$4.00

A solid, well documented account of the life and times of the first great physician of this country. The author deserves the gratitude of all who have been interested in the many-sided life of this medical man who was not only a medical educator, a professor of chemistry, a founder of temperance and antislavery societies, the first American psychiatrist, but also a great patriot and a courageous moulder of public

opinion in the Revolutionary period. A man of strong opinions, not unmixed with obstinacy, he made many enemies and had a historic falling out with Washington himself.

The author devotes separate chapters to various aspects of Rush's career. The account of the yellow fever epidemics is of particular interest. As a biographer the author does not yield to the modern temptation to dramatize the subject and the scene. But, if at times his narrative seems a little plodding, it is never dull and the reader feels that he is reading history and not journalism.

M C P

Diseases of the Heart. By JOHN COWAN, B A, M D, D Sc, F R F P S, and W I RITCHIE, O B E, M D, F R C P E, F R S E, with a chapter on The Occular Manifestations of Arterial Disease by ARTHUR J BALLANTYNE, M D, F R F P S. Third edition. xvi + 631 pages, 15 × 23 cm, 335 illustrations. William Wood and Co, Baltimore. 1935. Price, \$9.00.

This volume is not written in a particularly clear or concise fashion, and at times it seems rather disconnected. Too many briefly reported clinical cases are used to illustrate the text, often they do not particularly illuminate the point in question, and occasionally, in the reviewer's opinion, unwarranted deductions are made from such cases. There are many references to the extensive literature concerning the heart, and controversial matters are introduced without discussion adequate for a textbook. On the other hand some important viewpoints are not represented at all. High blood pressure and arteriosclerosis are not clearly separated, and there is no chapter on the former condition. In the therapeutic procedures considered will be found some which in this country are largely only of historic interest.

W S L, JR

What You Should Know about Heart Disease. By HAROLD E B PARDEE, M D. Second edition. 127 pages, 13.5 × 19.5 cm. Lea and Febiger, Philadelphia. 1935. Price, \$1.50.

This small volume is intended to help a heart patient understand his disease. It includes an explanation of the physiology and anatomy of the heart, discussions of various types of heart disease, including the arrhythmias. Symptoms are explained and there is discussion of the outlook for a patient with heart disease. Treatment is described, including drugs. The book is recommended to the attention of physicians who feel it desirable for certain heart cases to be more fully informed concerning heart disease.

W S L, JR

Krebs—im Lichte biologischer und zugleich anatomischer Forschung. I Band. By JOSEPH LARTSCHNEIDER, M D. Franz Deuticke, Leipzig and Wien. 1934.

This little volume of 192 pages and 48 illustrations is the first of a series of small books on cancer, written by Dr J Lartschneider, giving his experiences and studies over a period of forty years. The approach, as the title indicates, is from biological and comparative anatomical research.

The author gives an historical review of cellular pathology and compares it with the older theory of humoral pathology. He emphasizes that the cancer problem is still unsolved by cellular pathology and compares the attempt to explain cancer by this means to an architect who attempts to build a building with laborers only and without material. Humoral pathology which dominated the medical world for so many centuries, he likens unto an architect who attempts to build a building with material only.

and without labor. It is fortunate that humoral pathology came in contact with cellular pathology and thus collapsed. He warns, however, that cellular pathology dominates scientific medicine to the exclusion of other influences.

With these thoughts in mind the author discusses in the first volume various aspects of the problem of epidermal cancers (Ectodermkrebs). There are 13 chapters in all, the first being on the natural history of animal skin, giving also detailed consideration of human skin. The other chapters deal with such subjects as Strict Limitation of the Concepts of Epithelium, Waldeyer's Theory of Cancer, Physiological Epithelial Fusion and Physiological Bone Fusion, Rickets, Tooth Enamel and the Work Mode of Enamel Cells during Attacks of Rickets.

All of these subjects are presented in an interesting and new light, but the work is somewhat difficult to read on account of its intense detail. It is, no doubt, a definite contribution to the cancer problem.

A second volume in two sections has been received which will be given notice in a subsequent review.

G E W

COLLEGE NEWS NOTES

NLW LIFE MEMBERS

Dr Herman O Mosenthal (Fellow), New York City and Dr Carl H Gelenthien (Fellow) Valmoira N M, have recently become Life Members of the American College of Physicians

GIFTS TO THE COLLEGE LIBRARY

Dr J C Geiger (Fellow), Director of Public Health of the City and County of San Francisco—a copy of the manual entitled "Handbook of Accepted Remedies, Symptoms and Treatment of Poisoning Diagnostic Procedures, and Miscellaneous Information" This manual was prepared by Dr Geiger to serve as a guide in his department as well as for the use of the general profession

Acknowledgment is also made of the following gifts

Dr Linn J Boyd (Fellow), New York, N Y—a translation of Prof August Bier's "Contributions to the Physiology and Pathology of Circulation"

Dr Joseph Hajek (Fellow), New York, N Y—two reprints

Dr Carl R Howson (Fellow), Los Angeles, Calif—one reprint

Dr Frederick R Taylor (Fellow), High Point N C—one reprint

Dr Hyman I Goldstein (Associate), Camden, N J—one reprint

STATE MEETING OF BALTIMORE MEMBERS

Under the Governorship of Dr Henry M Thomas, Jr, Maryland members of the American College of Physicians conducted a state meeting at Baltimore on April 8, 1936 The program opened with a reception in the Board Room of the University Hospital, followed by a group of clinics in the Gordon Wilson Hall of the University Hospital and a dinner at the Hamilton Street Club The clinical program consisted of the following papers

"Pneumothorax Treatment of Pneumonia," Dr Harry M Stein, "A Case of Hair Dye Poisoning," Dr Raymond Peters, "Conditions Simulating Coronary Thrombosis in the Electrocardiographic Findings," Dr William S Love, Jr, "Hypertension Associated with Renal Tumor," Dr J Edmund Bradley, and "Multiple Apical Cavitations," Dr M C Pincoffs

At the dinner informal talks were given by Dr Sydney R Miller, past President of the College, by Dr M C Pincoffs Editor of the ANNALS OF INTERNAL MEDICINE, and by four or five other Fellows of the College The meeting was voted a great success and plans are being made to hold the next meeting in October 1936, at the Maryland State Tuberculosis Sanatorium at the invitation of Dr Victor Cullen (Fellow)

Under the Presidency of Dr Chesley Bush (Fellow), Livermore, and the Chairmanship of Dr Harold G Trimble (Fellow), Oakland, the California Tuberculosis Association held its annual meeting in Sacramento April 2 to 4, inclusive Dr J A Myers (Fellow), associate professor of preventive medicine in the Medical and Graduate Schools of the University of Minnesota, presented a paper entitled "The Contributions of Organization" Dr Sidney J Shipman (Fellow), San Francisco, delivered a paper, "Tuberculous Stenosis of the Bronchus," and Dr Edward Hayes

(Fellow), Monrovia, delivered a paper, "Relief Problems and Tuberculosis Control from the Viewpoint of a Physician" Other members of the College who officially appeared on the program as discussants of papers included Dr Benjamin W Black (Fellow), Oakland, Dr F M Pottenger (Fellow), Monrovia, Dr Samuel Hurwitz (Fellow), San Francisco, Dr Charles L Ianne (Associate), San Jose, Dr Mumford Smith (Fellow), Los Angeles, and Dr W C Voorsanger (Fellow), San Francisco

The Illinois Tuberculosis Association held its twenty-seventh annual meeting at Decatur, April 6 to 7 Dr D O N Lindberg (Fellow), superintendent and medical director of the Macon County Tuberculosis Sanatorium, delivered a paper on "The Role of the Chest Roentgenogram in Tuberculosis", Dr Robinson Bosworth (Fellow), superintendent and medical director of the Rockford Municipal Sanatorium, "Essential Considerations Affecting the Selection of Patients Who May Profit Most from Sanatorium Treatment, and Primary Reasons for Eliminating Certain Groups from the Sanatorium" Dr Gerald B Webb (Fellow), chief of medical staff, Sunnyside Sanatorium, Colorado Springs, Colo., delivered the banquet address, "An Outline of the History of Tuberculosis" Dr Cecil M Jack (Fellow), chairman of the Macon County Tuberculosis Sanatorium Board, presided at a luncheon and Dr F M Meiner (Fellow), President of the Peoria County Tuberculosis Association, presided at the medical session

Dr Austen Fox Riggs (Fellow), Stockbridge, Mass., has been appointed to the staff of the Williams College health department at Williamstown

Dr Sigmund S Greenbaum (Fellow) has been advanced from associate professor to professor of dermatology and syphilology, University of Pennsylvania Graduate School of Medicine

The following Fellows appeared on the program of general assemblies of the eighth annual spring conference of the Dallas Southern Clinical Society, March 16 to 19

Dr Francis G Blake, New Haven, Conn., "Treatment of Lobar Pneumonia", Dr Alan G Brown, Toronto, Ont., "Meeting the Nutritional Requirements of Infancy and Childhood", Dr Byrl R Kirklin, Rochester, Minn., "Diagnosis of Early Pulmonary Tuberculosis", and Dr John A Kolmer, Philadelphia, Pa., "Susceptibility, Immunity and Vaccination in Infantile Paralysis"

During February, at the regular clinical pathologic conference in the Peter Bent Brigham Hospital, Boston, Dr Henry A Christian (Fellow), Hersey professor of the theory and practice of physic at Harvard Medical School and physician-in-chief of the Peter Bent Brigham Hospital, was presented with a volume of medical papers dedicated to him by his former students, colleagues and house officers, as a token of affection on his sixtieth birthday Dr Francis G Blake (Fellow), Sterling professor of medicine at Yale University School of Medicine, New Haven, made the presentation

Dr Paul P McCain (Fellow), Sanatorium, N C., addressed the thirty-second annual meeting of the National Tuberculosis Association at New Orleans, April 22 to 25

Dr Lee D Cady (Fellow), St Louis, is President of the St Louis Medical Society

Dr Marcus W Newcomb (Fellow), Browns Mills, N J, is President of the Medical Society of New Jersey

Dr F M Pottenger (Fellow), Monrovia, Calif, is President of the Association for the Study of Internal Secretions

Dr Edward Weiss (Fellow) Philadelphia, has been advanced from clinical professor to professor of clinical medicine at Temple University School of Medicine

Dr Edgar Erskine Hume (Fellow) librarian of the Army Medical Library Washington, D C, addressed the New York Academy of Medicine on 'The Medical Work of the Knights of St John of Jerusalem' The program was arranged in co-operation with the section of historical and cultural medicine

Dr Joseph T Beardwood, Jr (Fellow), Dr Edward S Dillon (Fellow) and Dr Edward L Bortz (Fellow), all of Philadelphia, addressed the New York Diabetes Association, March 20 on the clinical aspects, complications and treatment of "Diabetic Acidosis," respectively The program of the clinical section was presented by the Philadelphia Metabolic Association

Dr Leonard G Rowntree (Fellow) delivered one of the lectures, "Organotherapy from the Internist's Viewpoint," in the thirty-sixth group of Mary Scott Newbold Lectures before the College of Physicians of Philadelphia on March 4

Dr John B Youmans (Fellow), associate professor of medicine, Vanderbilt University School of Medicine, Nashville, Tenn, has been appointed director of graduate courses, having special charge of courses given for practicing physicians with the cooperation of the Commonwealth Fund

Dr Karl D Figley (Fellow), Toledo, Ohio, recently addressed the Chicago Society of Allergy on "Iodized Oil in Intractable Asthma"

Dr John J Dumphy (Fellow), Worcester, Mass, addressed the New England Heart Association February 24 on 'Coronary Symptoms in Pernicious Anemia'

Announcement has been made that Dr Raymond B Allen, associate dean of graduate studies, Columbia University College of Physicians and Surgeons, New York, N Y, has been appointed dean of Wayne University College of Medicine, Detroit He will succeed Dr Walter H MacCracken (Fellow), who resigned a year ago In the meantime Dr William J Stapleton, Jr (Fellow), has been acting as dean Dr Stapleton will become associate dean

Dr Charles Walter Clarke (Fellow), New York City, has under his direction a special bureau in the Health Department for the control of venereal disease, functioning in connection with a campaign by the Department for the control of these diseases An appropriation of \$100,000 has been approved by the Works Progress Administration for this project

Dr David Riesman (Fellow), Philadelphia, delivered a lecture, "Diagnosis and Treatment of Early Circulatory Failure," in connection with the fourth annual clinical lectures of the Mercy Hospital

Georgetown University School of Medicine has added a course in medical social economics to its curriculum of the senior year. Among lecturers on the various phases of the subject appear the following Fellows

Dr Arthur C Christie
 Dr Oscar B Hunter
 Dr Henry C Macatee
 Dr J Russell Verbycke, Jr
 Dr Wallace M Yate

Dr James H Hutton (Fellow), Chicago addressed the Chicago Society of Industrial Medicine and Surgery recently on "Endocrinology in Industrial Medicine"

Dr Ira A Darling (Fellow), formerly superintendent of the Warren State Hospital, Warren, Pa, has been appointed superintendent of the Springfield State Hospital at Sykesville, Md

Dr W McKim Marriott (Fellow), dean and professor of pediatrics at Washington University School of Medicine, St Louis, recently directed a two weeks' graduate course in medicine given at Washington University the latter part of April for physicians in Calhoun, Barry, Branch, Eaton, Allegan, Hillsdale and Van Buren counties and Battle Creek, Mich, provided by the W K Kellogg Foundation, in connection with its community health project

Dr Anthony Bassler (Fellow), Dr Max Einhorn (Fellow) and Dr Samuel Weiss (Fellow), all of New York City, have been elected honorary members of the Belgian Gastro-Enterologic Society

Under the sponsorship of the Woman's Auxiliary of the Philadelphia County Medical Society, its sixth annual health institute was conducted on April 14. Among the speakers were the following Fellows, all of Philadelphia

Dr E J G Beardsley, "What Life Teaches the Doctor"
 Dr Martin E Rehfuss, "Diet After Forty"
 Dr Joseph C Doane, "Hearts and the Family Budget"
 Dr Louis H Clerf, "Household Aids to Health"
 Dr George E Pfahler, "Cancer—Increasing Hope for the Patient"
 Dr Samuel B Scholz, Jr, "Periodic Health Examinations"

Dr George W Covey (Fellow), Lincoln, Nebr, was inducted as President of the Nebraska State Medical Association at its annual meeting April 7

Dr Herbert L Bryans (Fellow), Pensacola, Fla, is one of a number of physicians selected to participate in the weekly radio program of lectures on medical economics, sponsored by the Florida Medical Association

Under the Presidency of Dr James E Paullin (Fellow), the Medical Association of Georgia held its annual session at Savannah, April 21-24. Dr William B Castle (Fellow), associate professor of medicine, Harvard Medical School, Boston, delivered the Abner Wellborn Calhoun Lecture on "Fundamental Aspects of the Diagnosis and Treatment of Anemia". Among other guest speakers were Dr James S McLester (Fellow), Birmingham President of the American Medical Association, "Influence of the Present Day Depression Upon the Nutritive State of the American

People" and Dr Jonathan C Meakins (Fellow), Montreal, former President of this College, "Management of the Chronic Heart"

Dr Carl H Gellenthien (Fellow), Valmora, N M, addressed the Des Moines Academy of Medicine and the Polk County Medical Society recently on "Practical Methods of Sanatorium Treatment of Pulmonary Tuberculosis"

The second annual graduate clinical meeting of the Alumni Association of the University of Buffalo School of Medicine took place April 18, and was addressed, among others, by Dr Walter C Alvarez (Fellow), Rochester, Minn, "Helpful Hints in the Diagnosis of Puzzling Types of Indigestion" and Dr Ernest E Irons (Fellow), Chicago, "Chronic Arthritis, a General Disease Requiring Individualized Treatment" Dr Reginald Fitz (Fellow), Boston, delivered the banquet address on "The Biography of the Famous Dr Watson of the Sherlock Holmes Stories"

Dr William Devitt (Fellow), director of Devitt's Camp for Tuberculosis near Allenwood, Pa, has been elected President of the Pennsylvania Tuberculosis Society

Dr Wallace M Yater (Fellow), Washington, D C, Dr William J Kerr (Fellow), San Francisco, Calif, and Dr Howard B Sprague (Fellow), Boston, Mass, were among the guest speakers on the program of the twelfth annual meeting of the American Heart Association in Kansas City, May 12

Under the Presidency of Dr George W Grier (Fellow), Pittsburgh, Pa, the American Radium Society held its annual meeting in Kansas City May 11 to 12 Dr George E Pfahler (Fellow), Philadelphia, as a former lecturer, received the Janeway Medal

Dr Joseph L Miller (Fellow), Chicago, Dr Ralph A Kinsella (Fellow), St Louis, Dr Philip S Hench (Fellow), Rochester, Minn, and Dr William J Kerr (Fellow), San Francisco, were among the speakers on the educational program on the differential diagnosis of diseases of joints at the meeting of the American Association for the Study and Control of Rheumatic Diseases at Kansas City, May 11

Dr Charles S Holbrook (Fellow), New Orleans, has been elected Vice President of the Southern Pediatric Association

Under the Presidency of Dr Morris Murray Peshkin (Fellow), New York City, the Association for the Study of Allergy held its annual meeting in Kansas City, May 11 to 12

Dr John G FitzGerald (Fellow), director of Connaught Laboratories and of the School of Hygiene, University of Toronto, has been appointed a member of the Permanent Commission of Biological Standardization of the Health Organization of the League of Nations

In recognition of his achievements in science, Dr James B Collip (Fellow), professor of biologic chemistry, McGill University Faculty of Medicine, was presented with a gold medal by the Royal Society of Canada at a meeting in Ottawa, during February

Dr Ralph Pemberton (Fellow), Philadelphia, appears on the program of the fifth International Congress on Rheumatism, to be held in Lund, Sweden, September 3 to 5, and in Stockholm, September 7 to 8



HARLOW BROOKS, M D

PRESIDENT OF THE AMERICAN COLLEGE OF PHYSICIANS, 1923 TO 1925

IN MEMORIAM

DR HARLOW BROOKS

Dr Harlow Brooks was born at Medo, Minnesota, on March 31, 1871. He received his preliminary education in the High School of Medo, and later graduated from the University of Oregon. In 1895 he received the degree M D from the University of Michigan School of Medicine, and from the same School received the honorary degree of M Sc in 1930. He took a postgraduate course of study at the University of Freiberg, and at the Polyclinic in Munich. He was Assistant Demonstrator of Anatomy at the University of Michigan School of Medicine in 1895, Instructor of Histology and Embryology, Bellevue Hospital Medical College, 1895-1898, Research in Bacteriology, New York State Hospitals, Pathological Institute, 1897-1920, Professor of Clinical Medicine, New York University Medical College, 1922-1929. At the time of his death he was Emeritus Professor of Clinical Medicine, New York University Medical College, Visiting Physician, Bellevue Hospital, Consulting Physician, New York City, French, New York Polyclinic, Union, Fifth Avenue, Hackensack, New Jersey, Beth Israel, Greenwich, Mount Vernon, Saint John's, Southside (Bay Shore), Flushing, Jamaica and Montefiore Hospitals, Hospital for Joint Diseases and Norwegian Lutheran, Deaconess's Home and Hospital. His World War record—Major, Lieut Colonel, and Colonel, M C, U S A, Chief of Medical Service base hospital, Camp Upton, Chief Consultant in Medicine First Army Corps, A E F, Senior Consultant in Medicine, Second Army Corps, A E F, awarded Distinguished Service Medal and a General Citation. He was a member of the American Legion and of the Association of Military Surgeons.

He was a member of Phi Alpha Sigma fraternity, member of the Harvey Society, Society of Experimental Biology and Medicine, Association of American Physicians, American Medical Association, American Gastroenterological Association, Medical Society of the State of New York, New York County Medical Society, and the American College of Physicians. He was elected Fellow of the American College of Physicians at its first regular meeting held in New York in December 1916. He was elected President in 1923 in which capacity he served for two years. In 1925 he was elected to the Board of Regents where he served for three years, in 1929 he was elected to the Board of Governors on which he served for two years. He also served on various committees and gave generously of his time and energies to the work of the College.

Dr Brooks was a prolific writer and published many monographs and special articles on medical and biological subjects. He was the Editor of Lippincott's Everyday Practice Series.

He was keenly interested in animal life, exploration, mountaineering and was an honorary Fellow in the New York Zoological Society and a

member of the Explorer's Club, Adventurer's Club, and the Camp Fire of America

He was one of the outstanding diagnosticians of his time and was called in consultation more frequently probably than any other doctor in the United States. He was looked upon as an authority in diseases of the circulatory system. He was often referred to as the doctor's doctor, being constantly sought by his brother practitioners in cases involving their immediate families, among whom he was known as the "Beloved Physician."

Few physicians of his time gave so generously of their services to the poor.

As a young pathologist, Dr. Brooks collaborated with Dr. William Welch at Bellevue Hospital in advanced research work that resulted in the discovery of the bacillus named after Dr. Welch which is responsible for the disease commonly called gas bacillus infection, and which, by a curious coincidence, was the cause of his death.

One of the contributing factors which enabled Dr. Brooks to maintain his enthusiasm for his profession and for life in general was his devotion to his hobbies which were varied. He was a skilled musician and a collector of outstanding works of art, as well as an anthropologist of note. His collection of Indian relics surpassed any similar private collection in the world, containing a few specimens not to be found in any other collection.

Probably his great physical stamina was due, in part at least, to his love for fishing and hunting, in each of which he was an outstanding expert. Often Dr. Brooks would remark that he gladly devoted ten months each year to the pursuit of his profession but retained two months to seek recuperation and happiness in the great open spaces.

One of the outstanding characteristics of this great physician was his genius for friendship. His friendship was a living vital force upon which rested profound gratification and innermost happiness. When Dr. Brooks bestowed his friendship it was for the duration of life. He was truly catholic in these friendships which were confined to no one profession or social stratum. Caring little for individual accomplishments, Dr. Brooks demanded honesty, frankness, and I was about to add, loyalty in his friends. However, since loyalty is the quintessence of true friendship it may be omitted.

I have somewhat stressed this phase of Dr. Brooks' character because to him it was the dominating influence of his life, and also because in these times of emotional upheaval and cross purposes the gift of true friendship is a God-given talent which is all too rare.

And so from out of our midst has been taken this great physician, this talented gentleman, this indefatigable worker, this scientist of renown, this man of many enthusiasms, of loyal friendships, of kindly heart and broad sympathies—gifted in so many ways and with so many talents that the world is richer for his having lived in it. Those who had the privilege of close

association with Dr Brooks will carry ever in their hearts the memory of his cheering and inspiring presence and the light of his Christian spirit

WILLIAM GERRY MORGAN

OBITUARIES

DR CHRISTOPHER M REYHER

Dr Christopher M Reyher (Fellow), of Gary, Indiana, met a tragic death in the path of a speeding train on February 12, 1936

Dr Reyher was born at Garfett, Ind , in 1881 He received his medical degree from Northwestern University Medical School in 1906 For many years he was engaged in general practice, but later specialized in pediatrics He was a member of the staffs of the Mercy and Methodist Hospitals, Gary, Ind , a member of the Lake County Medical Society, Indiana State Medical Association and the American Medical Association He became a Fellow of the American College of Physicians in 1925 He served as Secretary and later as President of the Board of Health of Gary and during his ten years in office made many important contributions to the public welfare

Dr Reyher was one of the best loved and most respected members of the medical profession in Gary His death brought forth expressions of regret and of tribute from all his colleagues as well as from a great host of patients to whom he had ministered during his twenty-six years of practice in that community

DR EDWARD QUINTARD

Dr Edward Quintard (Fellow), New York, N Y, physician and man of letters, died suddenly at the age of sixty-nine years on February 12, 1936 in Chattanooga, Tenn , where he had gone to attend a meeting of the Board of Regents of the University of the South Dr Quintard was a graduate of Columbia University College of Physicians and Surgeons, 1887 He was emeritus professor of medicine and consulting physician to the New York Postgraduate School and Hospital His influence and vision helped to guide this institution in its infancy After a broadly cultural education both here and in Europe, Dr Quintard first became attached to the New York Postgraduate School as clinical assistant He was rapidly promoted through the various grades and became professor of medicine in 1904 He had also served as director of the department of medicine for many years Also, in 1904, he was elected a member of the Board of Directors and served as Vice President until his retirement in 1918 He was a member of his local and national societies and had been a Fellow of the American College of Physicians almost from its inception, dating back to 1917 He made many important contributions to medical literature

His death brought personal sorrow to a large number in every walk of life Always a lover of good fellowship, Dr Quintard by his enthusiasm

and his mellow personality endeared himself to all who worked with him. In the latter years of his life, he gave great beauty to the world in his writing and painting, and was able to devote much time to literary and philosophical pursuits.

Selected, in part, from a resolution of the Board of Directors of the New York Postgraduate Hospital and furnished through the courtesy of Walter W. Palmer, M.D., F.A.C.P., Governor for eastern New York.

DR. ALBERT HARRISON BRUNDAGE

Dr. Albert H. Brundage (Fellow) of Woodhaven, Queens County, N. Y., died March 12, 1936, after many years of impaired health, aged seventy-three.

Dr. Brundage was born at Candor, Tioga County, New York, March 3, 1862. He graduated from the New York University Medical College in 1885. He held the additional degrees of A.M., Ph.D., Ph.D. and M.S. He was particularly interested in toxicology, being the author of "A Manual of Toxicology." For the last several years he had been consulting toxicologist in the Bushwick Hospital, medical inspector and lecturer in the Department of Health of the City of New York and a member of the auxiliary staffs of the Lutheran and Jamaica Hospitals. He became a Fellow of the American College of Physicians in 1929.

ANNALS OF INTERNAL MEDICINE

VOLUME 9

JUNE, 1936

NUMBER 12

DISTURBANCES OF THE ENDOCRINE BALANCE AND THEIR RELATION TO DISEASES OF METABOLISM *

By C N H LONG, M D , D Sc , *Philadelphia, Pennsylvania*

LAST year it was my privilege to address the College upon the subject of carbohydrate metabolism and the implications that recent work in this field had upon our knowledge of diabetes mellitus

Since this address appeared to meet with a certain measure of approval from you, I have ventured this evening to speak again upon certain pieces of work that to my mind are significant to those of us whose interest is concerned with the so-called diseases of metabolism

It appears to me that it is becoming more and more apparent that the clinical condition that follows hypo- or hyperfunction of an endocrine organ is not merely due to the loss or plethora of that particular internal secretion, but is a result of the disturbance of the normal hormonal equilibrium of the body

The work of the last few years has shown that the anatomical, and probably to a large extent the functional integrity of the majority of the endocrine organs, is dependent upon the anterior pituitary

The secretions of this gland either stimulate the production of hormones in the other endocrines or else enable these endocrines to maintain their secreting elements in such a condition that the production of their characteristic hormones becomes possible. There is then, in the truest sense of the word, an interrelationship between the anterior pituitary and the other organs of internal secretion. So widespread is the influence of the anterior pituitary over the whole endocrine system that at the present time it is difficult to consider any glandular interrelationship in which the possible participation of the anterior pituitary must not be allowed for

Thus it is becoming equally apparent that not only is the destruction of the anterior pituitary followed by a generalized endocrine atrophy, but also that removal of the gonads, thyroid or adrenals is followed by anatomical alterations in the anterior pituitary. These alterations are of such a striking

* Presented at the Detroit meeting of the American College of Physicians, March 2, 1936

From the George S. Cox Medical Research Institute, University of Pennsylvania, Philadelphia

ing character that it is difficult to conceive that they are not attended by equally significant changes in function. If this is so, then myxedema and Addison's disease should be considered not only as conditions dependent upon diminished thyroid or adrenaal cortical activity, but also from the point of view that an altered level of anterior pituitary function may be contributing to the clinical condition. In consequence, it becomes of some interest to discuss briefly the effects upon the anterior pituitary of the destruction or removal of the adrenals, thyroid and pancreas.

A The Adrenal Cortex Comparatively few observations are recorded upon the effect of adrenalectomy upon the anterior pituitary in animals, and these, probably on account of the stains employed, have yielded but little information. Recently, Crooke,¹ using a modification of the Mallory stain, has carefully studied this organ in 12 authenticated cases of Addison's disease. Not only was the general cytology examined, but in five cases a differential cell count was made. This author finds that the basophiles are greatly reduced in number along with a variable degree of reduction of the acidophiles. These changes were found in one individual even after treatment with cortical extract for 19 months. Crooke has suggested that this loss of basophiles may be associated with the hypoglycemia that is such a constant feature of this disease. This is supported by his later observation that hyperactivity of the basophiles such as is observed in pituitary basophilism is associated with an elevated blood sugar.

In view of the striking alterations induced in the anterior pituitary as a result of destruction of the adrenal cortex it would be surprising if this organ retained its normal degree of function. Grollman's² experiments upon adrenalectomized rats maintained with minimal doses of cortical extract indicate that the failure of growth and reproductive function in chronic adrenal insufficiency is due to hypofunction of the anterior pituitary. Such animals will grow again only if given pituitary extracts rich in the growth promoting principles. The injection of potent adrenaal cortical extracts is at this time incapable of restoring normal growth. Histological examination of the anterior pituitary of such animals reveals a diminution of both the basophilic and acidophilic cells, the former undergoing the greatest change.

B The Thyroid Numerous studies have been carried out upon the changes in the anterior pituitary following thyroidectomy in animals and in cases of human hypothyroidism. Practically all authors are agreed that the acidophiles are greatly reduced, while certain authors have observed alterations in the basophiles. Zeckwei and her co-workers³ have recently published an excellent paper upon the alterations in the anterior pituitary of young thyroidectomized rats. They find that in all cases where the rats have become stunted in growth the acidophiles had practically disappeared while the basophiles had undergone remarkable changes, becoming enlarged, vacuolated, and containing hyaline material. Zeckwei has made the interesting and probably correct suggestion that the cessation of growth in these young thyroidectomized rats is a consequence of the reduction of the

acidophilic elements of the pituitary. It would be of great interest to know if the administration of anterior pituitary extracts would cause these cretin rats to resume growth.

The above results clearly show that destruction or removal of the adrenals or thyroid causes marked structural alterations in the anterior pituitary. In addition to these anatomical changes evidence is also accumulating that certain aspects of the deficiency, usually attributed to the loss of the thyroid or adrenal secretion, are in reality to be attributed to the concomitant pituitary dysfunction.

Diabetes mellitus is a disease of metabolism that is at present held to be due to hypofunction of the islands of Langerhans. In view of the alterations induced in the anterior pituitary by hypofunction of the adrenals and thyroid it is surprising that so few histological studies of this organ in diabetes have been made. However, Fry⁴ and Kraus⁵ have reported that following pancreatectomy in animals, or in human diabetics, there is present a proliferation of eosinophiles and an accumulation of colloid material. On the other hand, Warren was unable to confirm such changes in the pituitaries of the diabetics he studied.

There is no doubt, however, of the striking effects of hypophysectomy upon an experimental diabetes, and in view of the bearing of these findings upon the problem of glandular interrelationships and disturbances of the metabolic processes it is necessary to consider in some detail the factors known at present to influence the diabetes of a totally depancreatized animal.

FACTORS MODIFYING AN EXPERIMENTAL DIABETES

As I pointed out last year, the demonstration by Houssay and Biasotti⁶ that hypophysectomy greatly alters the response to total pancreatectomy in animals necessitates a revision of our previous ideas, not only upon the mechanism by which experimental diabetes is produced but also upon the factors normally operating to control the protein, fat and carbohydrate metabolism of the body.

There are three major factors which, when in equilibrium, result in what we speak of as a normal metabolism. These are (a) the secretions of the various endocrine organs, (b) the liver, and (c) the tissues. Disturbance of any of the former such as follows the extirpation of an endocrine organ is followed by a condition in which not only is the metabolic equilibrium disturbed by the loss of this particular secretion, but also by the uncompensated activity of the remaining glands.

The interest excited by the effects of the anterior pituitary hormones upon metabolism should not lead us to neglect the fact that the liver is in all probability the organ upon which their influence is mainly exerted. It is this organ that is the site of glucose formation and probably of the major processes of fat metabolism. Thus, as Mann and Magath,⁷ and Yater, Markowitz and Cahoon⁸ have shown, removal of the liver even from a

totally depancreatized dog results in a rapid fall of the blood sugar, and Campos⁹ has demonstrated that in hepatectomized toads potent anterior pituitary extracts do not exert their usual effect of increasing the blood sugar.

Finally the metabolism of the tissues themselves can be greatly modified by various hormones. Insulin increases their utilization of carbohydrate while epinephrine diminishes it. The effect of the anterior pituitary hormones upon the metabolism of the tissues is a subject which so far has not been investigated. It may well be that one of the factors reducing carbohydrate utilization after pancreatectomy is not entirely the absence of insulin, but is in large part due to the inhibition of glucose oxidation by the pituitary hormones themselves.

Thus it is not surprising that as investigation proceeds a number of conditions are being found by which the usual effects of pancreatectomy can be modified. These can be roughly divided into

(a) *Alterations of the endocrine balance*

- (1) Hypophysectomy (Houssay⁶)
- (2) Adrenalectomy (Long and Lukens¹⁰)

(b) *Disturbances of liver function*

- (1) Complete or partial hepatectomy (Mann and Magath⁷)
- (2) Marked fatty infiltration such as follows the giving of low choline diet to a depancreatized animal maintained on insulin (Best et al¹¹)

(c) *Tissues*

Reduction of body weight by fasting (Allen¹²)

(d) *Lesions of the hypothalamus*

It has been reported by Davis, Cleveland and Ingram¹³ that cats depancreatized after placing suitable lesions on the hypothalamic area exhibit a modified diabetes. Whether such lesions exert their effect by interference with the function of the anterior pituitary or whether they interrupt nervous pathways concerned with metabolic processes remains to be decided.

THE RELATION OF THE ABOVE FINDINGS TO HUMAN DIABETES

In the experimental work cited above the pancreas has been removed before or after the establishment of one of the conditions outlined above. Thus the diabetes studied has been of primary pancreatic origin. It is obvious, however, that the chief interest from a clinical point of view would be in the establishment of the fact that alterations in the functional activity of certain endocrine organs, the liver or central nervous system, could give rise to diabetes mellitus. Now it will be recalled that for many years the view has been held that all cases of diabetes mellitus in man were the result of hypofunction of the islands of Langerhans, and it should also be emphasized that the majority of autopsies upon diabetics disclose pathological

changes in these structures. Nevertheless this unitarian view of the etiology of diabetes in man has not been universally accepted.

Since it has been demonstrated that the removal of the hypophysis or adrenals will modify an existing pancreatic diabetes it is profitable to examine the effects upon carbohydrate metabolism of conditions in which there exists hyperactivity of the anterior pituitary or adrenal cortex.

One of these conditions is acromegaly in which there is present a functioning tumor of the anterior pituitary. In these individuals, as has been repeatedly shown, glycosuria and often frank diabetes are of common occurrence.

Of recent years the extraordinary condition commonly known as "Cushing's syndrome" or pituitary basophilism has received an increasing amount of attention. Although the first cases described by Cushing were associated with a small basophilic adenoma of the anterior pituitary, it is now recognized that in adults the same condition is produced by the presence of an adrenal cortical carcinoma or adenoma. Recently this paradox has been further complicated by the report of three individuals with tumors of the thymus gland who also exhibited this interesting clinical picture.

Lukens and I have examined the records of 20 cases of this syndrome associated with proved basophile adenomas of the pituitary. Of these, 14 exhibited glycosuria. A similar study of 55 cases of proved adrenal cortical tumor or hyperplasia showed that half of them had a demonstrable impairment of carbohydrate tolerance. Finally, all three cases of Cushing's syndrome associated with thymic tumors exhibited glycosuria.

It is obvious from a study of these cases that there exists a generalized glandular derangement, and it is important for an understanding of the glycosuria that is found to investigate what endocrine disturbance is common to these three types of cases. (a) In basophilic adenomas of the pituitary hypertrophy of the adrenal cortex, often reaching a marked degree, is common. (b) In the cases associated with adrenal cortical tumor or hyperplasia it has heretofore been assumed that the hyperactivity of this organ was responsible for the condition observed. (c) In all three reported cases of thymic tumor the adrenal cortex has been enlarged.

These findings, together with the fact that total adrenalectomy is effective in reducing the glycosuria of a depancreatized animal, suggest that the glycosuria observed in the above groups is associated with hyperactivity of the adrenal cortex. Here, however, we cannot rest, since last year Crooke,¹⁴ in an excellent cytological study of the anterior pituitary of six cases of basophilic adenoma, three of adrenal cortical carcinoma and three of thymic tumor, has demonstrated that in all instances the basophile cells were the site of a curious hyaline change. Since this hyaline change is presumably demonstrable in all cases of Cushing's syndrome and since hyperplasia of the adrenal cortex, although very common, is not invariably present, we are forced to conclude that a direct association between hyperactivity of the adrenal cortex and glycosuria has not yet been established.

It may well prove to be that several causes, among them adrienal cortical or thymic hyperactivity, may precipitate this activation of the anterior pituitary. Once this is established a generalized glandular derangement follows, one result of which is glycosuria, and not infrequently clinical diabetes mellitus.

Nevertheless these facts do not answer our original enquiry as to whether individuals without acromegaly or Cushing's syndrome ever develop diabetes mellitus as a consequence of pituitary dysfunction. All the evidence gathered from the effects of various procedures upon experimental diabetes together with that obtained from a study of cases with undisputed pituitary or adrienal dysfunction, although highly suggestive of such an etiology in at least some diabetics, is by no means conclusive. It would, however, appear to offer an advantageous method of approach to the study of the etiological basis of the disease in man.

FACTORS DETERMINING GLUCOSE TOLLRANCE

Himsworth,¹⁵ in a well documented and ingeniously argued series of papers, has advanced the view (a) That the response of the blood sugar of normal individuals to the ingestion of glucose is determined solely by the carbohydrate content of the diet previous to the test. With a low carbohydrate diet the curves indicate a decreased tolerance to ingested glucose, but as the proportion of dietary carbohydrate is increased, curves indicative of an improving glucose tolerance are obtained. (b) The sensitivity of the individual to a given amount of insulin increases with the amount of carbohydrate in the diet. (c) It is commonly assumed that when glucose is ingested the supply of insulin is temporarily increased to meet this circumstance. Himsworth points out that this supposition is unnecessary since his work indicates that increasing the amount of carbohydrate in the diet increases the efficiency of the usual supply of insulin to such an extent that the additional carbohydrate is easily disposed of. In consequence it is unnecessary to postulate variations in insulin secretion in response to carbohydrate ingestion. As will be seen shortly, Soskin et al.,¹⁶ from an entirely different type of experiment, have arrived at similar conclusions. These views are of course at variance with those of other workers, particularly Zuntz and LaBarre,¹⁷ and it would appear that the stage is set for a controversy similar to that waged over the continuous or intermittent secretion of epinephrine. (d) Of even greater interest are Himsworth's views as to the reason for the greater efficiency of insulin when a large amount of carbohydrate is being ingested. He has advanced the hypothesis that insulin as secreted by the pancreas is physiologically inactive and requires the presence of an activator, probably supplied by the liver, in order to bring out its well known effects upon carbohydrate utilization. He implies that a large carbohydrate intake favors the production of the "activator" while low carbohydrate diets inhibit its production. Now it will be apparent that if

this view is correct, diabetes could occur in an individual with a normal insulin supply as a result of a deficient quantity of insulin activator

On the basis of this hypothesis, Himsworth has attempted to classify human diabetes into two groups (*a*) insulin sensitive, and (*b*) insulin insensitive. The former are those in whom a deficiency of insulin production by the pancreas is the essential defect. These individuals are those in whom injected insulin is highly effective, and furthermore are the group of diabetics who are most likely to tolerate a high carbohydrate-low fat diet without any increase in insulin requirements.

The insulin insensitive group, on the other hand, are those individuals who will not tolerate an increase in carbohydrate intake unless the insulin supply is correspondingly increased. Himsworth believes that the insulin insensitive group of diabetics are those in whom insulin deficiency is not the primary cause of the disease, but are diabetic because of a deficiency of some substance which in normal individuals is essential for the proper action of insulin.

Soskin and his co-workers,¹⁶ although in agreement with Himsworth that the pancreas does not secrete an increased amount of insulin after glucose ingestion, disagree with him upon the question as to whether insulin requires to be activated before it becomes physiologically effective in the body.

These workers hold that when the blood sugar level falls below a certain value the formation of glucose in the liver from non-carbohydrate sources (gluconeogenesis) is stimulated, and conversely, when the blood sugar level rises above a certain point, the amount of gluconeogenesis is decreased. Furthermore, it is held that this capacity of the liver to regulate the formation of glucose in accordance with the needs of the body is normally under the control of the opposing influences of the hormones of the pancreas and hypophysis. Their experimental work has led them to the conclusion that the variable factor in this endocrine balance is not the supply of pancreatic insulin but the amount of liver gluconeogenesis and consequently the amount of hypophyseal activity. Therefore, when glucose is ingested the ensuing changes in the blood sugar curve are not the result of an increased secretion of insulin, but are determined by alterations in the amount of glucose formation by the liver.

When this hypophyseal-pancreas-liver relationship is disturbed by pancreatectomy, then excessive gluconeogenesis continues during glucose ingestion and a diabetic tolerance curve results, conversely, when the hypophysis is removed, the marked decrease in the gluconeogenetic processes renders the organism insulin sensitive and increases the tolerance to glucose. When both pancreas and hypophysis are excised an intermediary level is established at which point "normal" tolerance curves may be found.

In view of this work, along with that of Houssay and others, it appears that other reasons than lack of an insulin activator might be ascribed to cases of insulin-insensitive diabetes. Thus it has been established (*a*) that hypo-

physcctomized animals are insulin sensitive, (b) such animals have an increased carbohydrate tolerance, (c) normal animals may be rendered insulin insensitive by the injection of anterior pituitary extracts even though the composition of the diet remains unchanged, and (d) such injections decrease their carbohydrate tolerance. Therefore, instead of invoking a hypothetical insulin activator, is it not more reasonable to say that the anterior pituitary hormones play a conspicuous rôle in determining the response of the organism not only to ingested carbohydrate, but also to exogenous and endogenous insulin?

It may thus be postulated that Himswoth's insulin sensitive group of diabetics are those (as he himself has pointed out) in whom the defect is an inadequate supply of insulin, while the insulin insensitive group are those diabetics in whom a relative preponderance of hypophyseal activity is the exciting cause of the disease even though their supply of pancreatic insulin remains within normal limits.

I wish, however, to emphasize that no experimental work supporting a classification of diabetes along these lines has yet appeared, nor has any evidence yet been adduced that in certain diabetics the hypophyseal or adrenal function is deranged.

The interest of these experiments, apart from the fact that they ascribe an extra-pancreatic origin to certain cases of diabetes, lies in the concept that the response of the organism to such a physiological process as the ingestion of carbohydrate is determined not by the liver, pancreas or tissues acting alone, but by a response that necessitates the readjustment of an equilibrium that is normally maintained by the activity of the endocrine organs. Thus, of course, is merely a restatement of the principle of homeostasis that the work of Cannon¹⁸ has done so much to disclose.

Long continued disturbances of this equilibrium such as are induced by chronic hyper- or hypofunction of one or more endocrine organs, result in conditions which are clinically spoken of under such names as Graves' disease or Addison's disease. While it is obvious that acute deprivation of any particular hormone may result in death before any secondary consequences can be established, this is not the condition that is usually encountered in man.

It is my belief that a better understanding of the diseases of metabolism that are associated with a disturbed endocrine function can be reached by ceasing to regard them merely as an expression of the effects of alterations in function limited to one endocrine organ, but rather in the light of our newer knowledge of the close interrelationship between all the organs of internal secretion.

These remarks should not be interpreted as endorsing ill-timed surgical assaults upon the pituitary and adrenals either in the case of hyperthyroidism or diabetes mellitus, since as I have previously pointed out, no evidence is yet available that these organs are primarily involved in the appearance of these diseases in man.

BIBLIOGRAPHY

- 1 CROOKE, A C, and RUSSELL, D S The pituitary gland in Addison's disease, *Jr Path and Bact*, 1935, vi, 255
- 2 GROLLMAN, A and FIROR, W M Role of the hypophysis in experimental chronic adrenal insufficiency, *Am Jr Physiol*, 1935, cxii, 310
- 3 ZECKWER, I, DAVISON, L W, KELLER, T B, and LIVINGOOD, B S The pituitary in experimental cretinism I Structural changes in the pituitaries of thyroidectomized rats, *Am Jr Med Sci*, 1935, cxc, 145
- 4 FRY, H J B The pituitary gland in diabetes mellitus and disorders of the glands of internal secretion, *Quart Jr Med*, 1915, viii, 277-299
- 5 KRAUS, E J Hypophyse und Diabetes mellitus, *Virchow's Arch f path Anat*, 1920, ccxxviii, 68-133
- 6 HOUSSAY, B A, and BIASOTTI, H Hypophysis, carbohydrate metabolism and diabetes, *Endocrinology*, 1931, xv, 511
- 7 MANN, F C, and MAGATH, T B The effect of removal of the liver after pancreatectomy on the blood sugar level, *Arch Int Med*, 1923, xxxi, 797
- 8 YATER, W M, MARKOWITZ, J, and CAHOON, R F Consumption of sugar by muscle in the non-diabetic and diabetic state, *Arch Int Med*, 1933, li, 800
- 9 CAMPOS, C A, CURUTCHET, J L, and LANARI, A Role du foie dans l'action diabéto-gène du lobe glandulaire de l'hypophyse de crapaud, *Compt -rend Soc de biol*, 1933, cxiii, 467
- 10 LONG, C N H, and LUKENS, F D W The effect of adrenalectomy and hypophysectomy upon experimental diabetes in the cat, *Jr Exper Med*, 1936, lxiii, 465
- 11 BEST, C H, FERGUSON, G C, and HERSHEY, J M Choline and liver fat in diabetic dogs, *Jr Physiol*, 1933, lxxix, 94
- 12 ALLEN, F M Glycosuria and diabetes, 1913, Harvard University Press
- 13 DAVIS, L, CLEVELAND, D, and INGRAM, W R Effect of hypothalamic lesions and stimulation of autonomic nervous system upon carbohydrate metabolism, *Arch Neurol and Psychiat*, 1935, xxxiii, 592
- 14 CROOKE, A C A change in the basophile cells of the pituitary common to conditions which exhibit the syndrome attributed to basophile adenoma, *Jr Path and Bact*, 1935, vi, 339
- 15 HIMSWORTH, H P
 - (a) Physiological activation of insulin, *Clin Sci*, 1933, i, 1
 - (b) Dietetic factors influencing glucose tolerance and activity of insulin, *Jr Physiol*, 1934, lxxxi, 29
 - (c) Influence of diet on sugar tolerance of healthy men and its reference to certain extrinsic factors, *Clin Sci*, 1934, i, 251
 - (d) Dietetic factor determining glucose tolerance and sensitivity to insulin of healthy men, *Clin Sci*, 1935, ii, 67
 - (e) Diabetes mellitus its differentiation into insulin-sensitive and insulin-insensitive types, *Lancet*, 1936, ccxxx, 127
- 16 SOSKIN, S, ALLWEISS, M D, and COHN, D J Influence of the pancreas and the liver upon the dextrose tolerance curve, *Am Jr Physiol*, 1934, cix, 155
- 17 ZUNTZ, E, and LABARRE, J Sur l'augmentation de la teneur en insuline du sang veineux pancreatique apres l'hyperglycemie provoquee par injection de glucose, *Compt -rend Soc d biol*, 1927, xcvi, 421
- Sur la sensibilité des centres nerveux superieurs a l'hyperglycemie provoquee par l'injection de dextrose, *Compt -rend Soc d biol*, 1927, xcvi, 1400
- 18 CANNON, W B Stresses and strains of homeostasis, *Am Jr Med Sci*, 1935, clxxix, 1

A COMPARISON OF THE EFFECTIVENESS OF GLUTAMIC ACID HYDROCHLORIDE AND DILUTE HYDROCHLORIC ACID AS THE REPLACEMENT THERAPY IN ANACIDITY MEASURED BY FRACTIONAL GASTRIC ACID TITRATION AND HYDROGEN-ION CONCENTRATION CURVES

By HARRY SHAY, M D , and J GERSHON-COHEN, M D , M Sc (Med),
Philadelphia, Pennsylvania

For the most part, anacidity has been regarded an interesting but scarcely serious medical curiosity. In the absence of gastric carcinoma, or of blood changes suggestive of Addisonian anemia, little consideration has been generally given the anacidity. In fact, since the work of Castle,¹ it has progressively diminished in importance as a factor in anemia. Clinically, spectacular therapeutic results have been obtained from the administration of hydrochloric acid for the relief of vague, but distressing, digestive symptoms, or in the more obvious gastrogenous diarrhea. Experimentally, time and effort have been lavished upon the study of the response of the achlorhydric to histamine and to the ability of the anacid stomach to secrete parenterally injected neutral red, but small thought indeed has been given to the possibility of a far-reaching and insidious effect of anacidity upon the body's physiology.

Numerous papers have pointed out the relatively higher incidence of anacidity in cholecystitis, diabetes, arthritis, and their like, but the likelihood of anacidity being cause rather than effect has gone almost completely unsuspected. We believe this relationship will become evident when the physiology of the upper small intestine is completely understood.

Scattered evidence is now available, and more is certain to be added, to show that the duodenum is rivalled only by the pituitary as the source for a multiplicity of hormones with many, and extended, physiological effects. Further, the trigger that sets this off is the arrival of the gastric hydrochloric acid into the duodenum. We attribute this action to the hydrochloric acid as the intrinsic agent. It is not, however, the sole agent capable of inaugurating the reaction, for any substance that can alter the osmotic conditions in the duodenum away from isotonicity will activate the duodenal mucosa to a greater, or a lesser, degree.

Forgetting for a moment the action of the gastric hydrochloric acid in initial protein digestion, or as a bactericide, let us examine the part it might play upon its entrance into the duodenum. We need only recall its rôle in

* Received for publication January 3, 1936.

To Mr Samuel S. Fels the authors are deeply grateful for his active cooperation in these investigations. Mr Fels not only made the grant under which the studies were originated and carried through, but at weekly conferences contributed much of real value to the studies.

the crucial experiment of Bayliss and Starling,² using the denervated isolated jejunal loop to demonstrate the hormonal mechanism for the external secretion of the pancreas. Gastric hydrochloric acid as the intrinsic agent supplying the stimulus in the duodenum and upper jejunum in the production of a substance capable of diminishing the blood-sugar concentration, has been suggested since the work of Freud and Saadi-Nazim³ in dogs in 1926. Whether this is due to another hormone which stimulates the pancreatic islets, or whether hydrochloric acid itself is able to modify a raised blood-sugar level, or whether both mechanisms are operative is, so far, not entirely clear. We are about to publish data which demonstrate this mechanism for man and which indicate the separate action rather than the islet stimulation. In his discovery of cholecystokinin, Ivy⁴ has shown the relationship of the gastric acid to gall-bladder emptying. Recently, we⁵ demonstrated the importance of the same acid as the intrinsic agent in the duodenum which acts as the control of the local mechanism concerned with gastric evacuation. It is also likely from our studies of the motor function of the resected stomach⁶ that the gastric motor inhibitory hormone conceived in the work of Farrell and Ivy,⁷ Lim,⁸ Quigley,⁹ and their co-workers is dependent for its intrinsic motivation upon the hydrochloric acid of the stomach. The importance of this acid in the absorption of calcium from the intestine was recently graphically demonstrated by Ivy¹⁰ in the bone changes produced in young and adult dogs after gastrectomy.

Thus, because of the manifold and extended effects of which it is possibly the source, anacidity demands more interest than a cursory one in its etiology and in its replacement therapy—which is for the present quite simply, the attempt to simulate as accurately as possible a normal gastric acid curve.

METHOD

Fourteen patients with anacidity were studied. Nine remained anacid after histamine. Fractional gastric analysis was used throughout. The patients reported after an overnight fast. The fasting gastric contents were removed through a Rehfuess tube, and then the test meal, which consisted of 20 grams of zweiback and 300 c c of distilled water, was ingested. The gastric response to this meal was first determined, specimens being removed at quarter-hour intervals for two hours, or until the stomach was empty. Each specimen was titrated for free acid to dimethylamidoazobenzol and for total acid to phenolphthalein, and recorded in the usual manner in c c of tenth normal acid per 100 c c of gastric contents. Hydrogen-ion concentration was determined with the quinhydrone electrode.

The same patients were then studied after addition of varying amounts of dilute hydrochloric acid to the water before ingestion of the meal. A dropper was used for measuring the acid in order more closely to simulate the clinical method of administration. This dropper yielded 16 drops to the c c. Glutamic acid and glutamic acid hydrochloride were administered

in capsules (0.31 gram each) in two portions, one-half when half the test was taken, and the other half at the end of the meal. Extractions and determinations were carried out as with the *weiback-and-water* meal. One hundred and four fractional analyses were made on the 14 patients.

DISCUSSION

Replacement therapy in anacidity has pretty generally taken the form of hydrochloric acid. Some years ago, Arthur F. Hurst¹¹ recognized the inadequacy of the official pharmacopoeial dosage and advocated quantities of 4 to 6 c.c. which was, and still is, considered by many to be a radical recommendation. Later, Crohn,¹² and Kern, Rose, and Austin¹³ demonstrated the failure of the usual therapeutic doses of dilute hydrochloric acid to modify intragastric acidity in achlorhydria. Superficially the usual doses are found to be therapeutically efficient, but when measured by actual titration and hydrogen-ion determinations in fractional gastric studies, it is surprising to see how ineffective massive doses are to establish even an approach

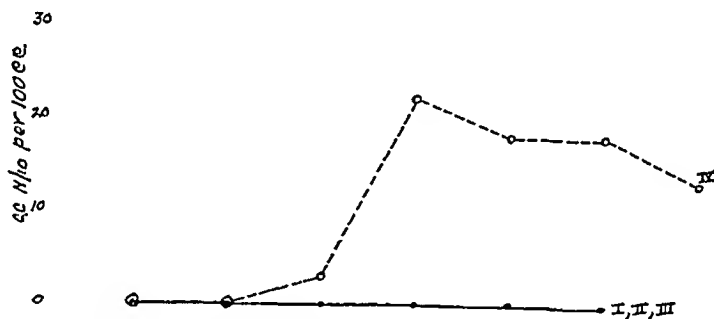


CHART 1 Case S. L. I Free acid titration curve after Ewald meal. II Free acid titration curve after Ewald meal plus 80 drops dilute HCl. III Free acid titration curve after Ewald meal plus 4 capsules glutamic acid. IV Free acid titration curve after Ewald meal plus 4 capsules glutamic acid HCl.

to what would be considered a normal gastric acid response. (See charts.) An amount of hydrochloric acid as large as 120 to 160 drops (7.5 to 10.0 c.c.) added to the Ewald meal (charts 5 and 7) produced a low free acid curve during the fractional analysis, while 80 drop portions (5 c.c.) were usually inadequate to show any free acid to Topfer's reagent at any time (charts 1, 5, and 7). The results obtained in the hydrogen-ion concentration curves confirmed the titration values insofar as the addition of smaller quantities of the acid to the meal failed to produce a pH reading below 3.5, at which point free acid will be demonstrated by Topfer's reagent. (Charts 3, 4, and 7.) (In several thousand pH determinations on gastric samples with the quinhydrone electrode, we have always obtained a free acid reaction to Topfer's when the pH reading was below 3.5.) It would appear, therefore, that the therapeutic effects derived from the administration of the usual dosage of hydrochloric acid are definitely not dependent upon the

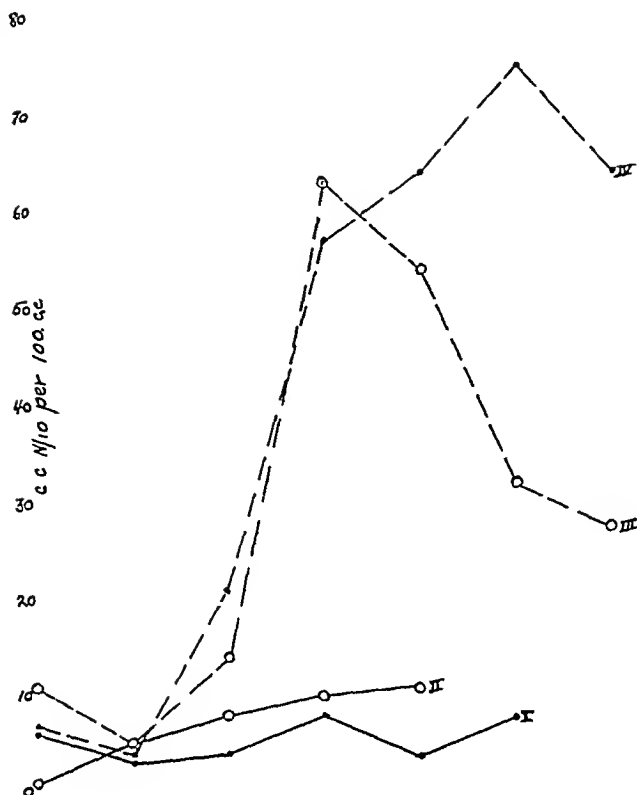


CHART 2 Case S L I Total acid titration curve after Ewald meal II Total acid titration curve after Ewald meal plus 80 drops dilute HCl III Total acid titration curve after Ewald meal plus 4 capsules glutamic acid IV Total acid titration curve after Ewald meal plus 4 capsules glutamic acid HCl

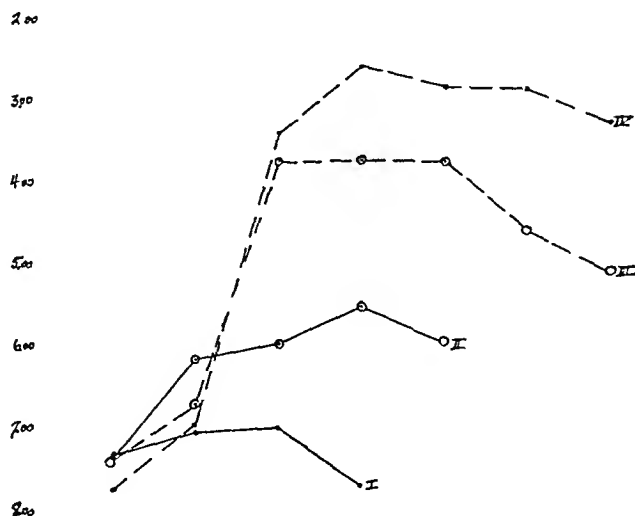


CHART 3 Case S L I Curve of pH after Ewald meal II Curve of pH after Ewald meal plus 80 drops dilute HCl III Curve of pH after Ewald meal plus 4 capsules glutamic acid IV Curve of pH after Ewald meal plus 4 capsules glutamic acid HCl

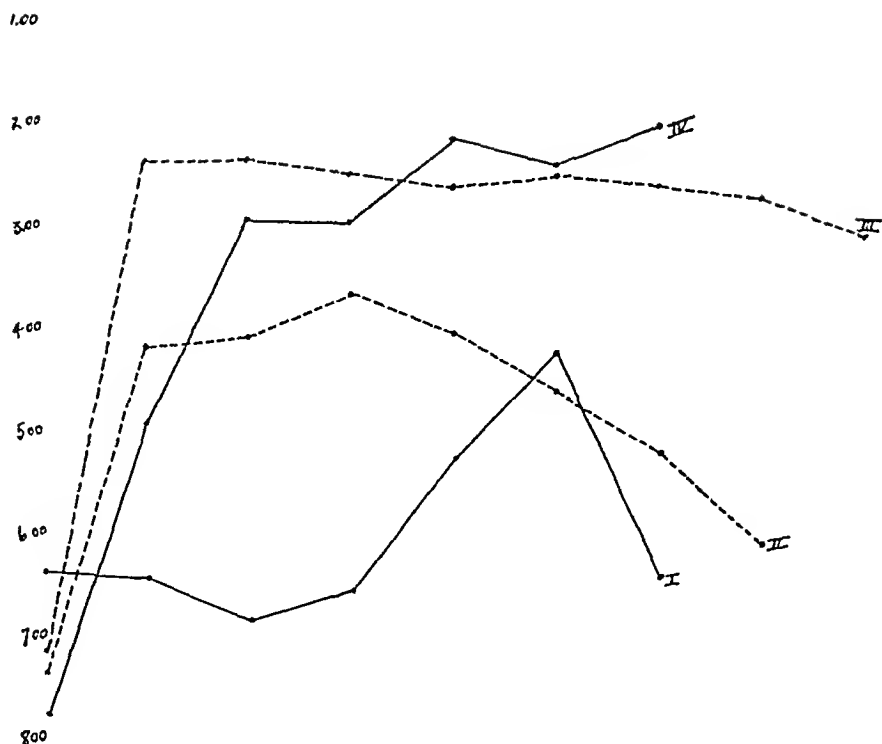


CHART 4 Case L F I Curve of pH after Ewald meal II Curve of pH after Ewald meal plus 80 drops dilute HCl III Curve of pH after Ewald meal plus 160 drops dilute HCl IV Curve of pH after Ewald meal plus 4 capsules glutamic acid HCl

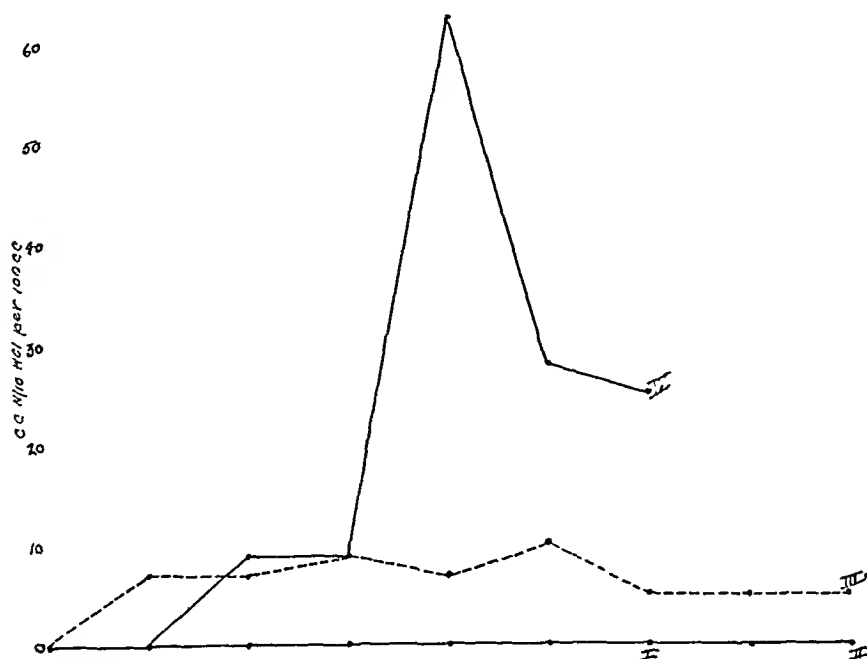


CHART 5 Case L F I Free acid curve after Ewald meal II Free acid curve after Ewald meal plus 80 drops dilute HCl III Free acid curve after Ewald meal plus 160 drops dilute HCl IV Free acid curve after Ewald meal plus 4 capsules glutamic acid HCl

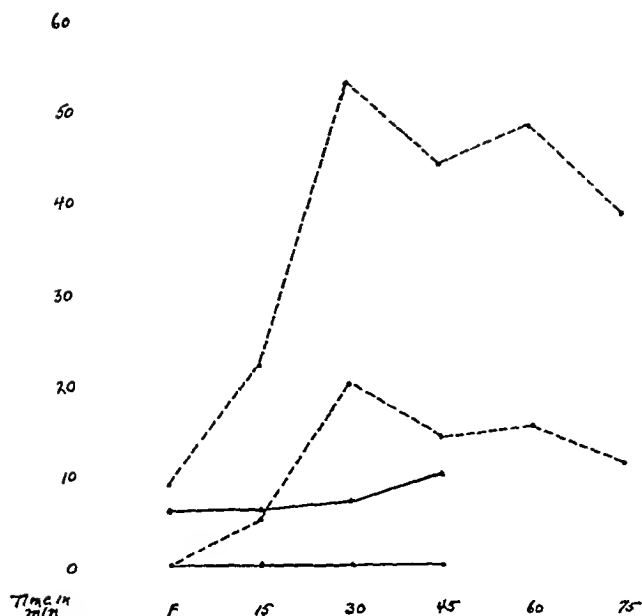


CHART 6 Case M M F ——— Free and total acid curve after Ewald meal + 60 drops dilute HCl - - - - - Free and total acid curve after Ewald meal + 2 capsules glutamic acid HCl

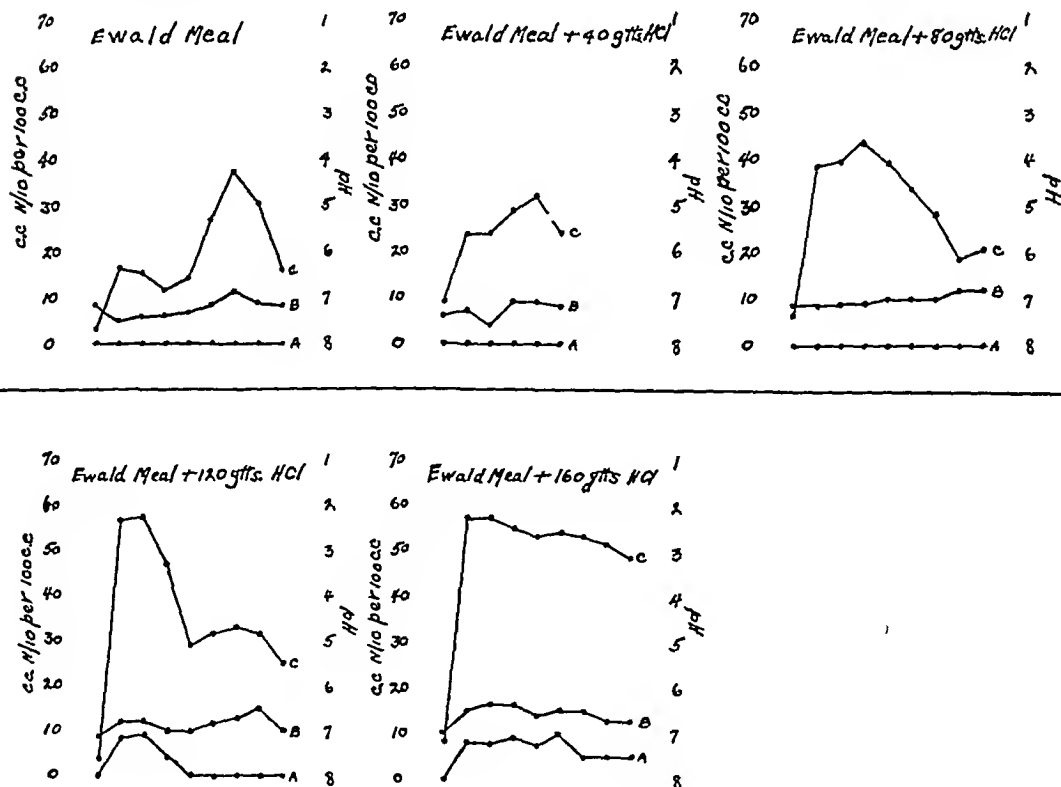


CHART 7 A = curve of free HCl B = curve of total acidity C = curve of pH

presence in the stomach of any free acidity at the time of digestion. From our experiences with the rôle of the hydrochloric acid in the duodenum, we venture the opinion that the beneficial clinical results are caused by the altered osmotic conditions produced in the upper intestine by the administered acid.

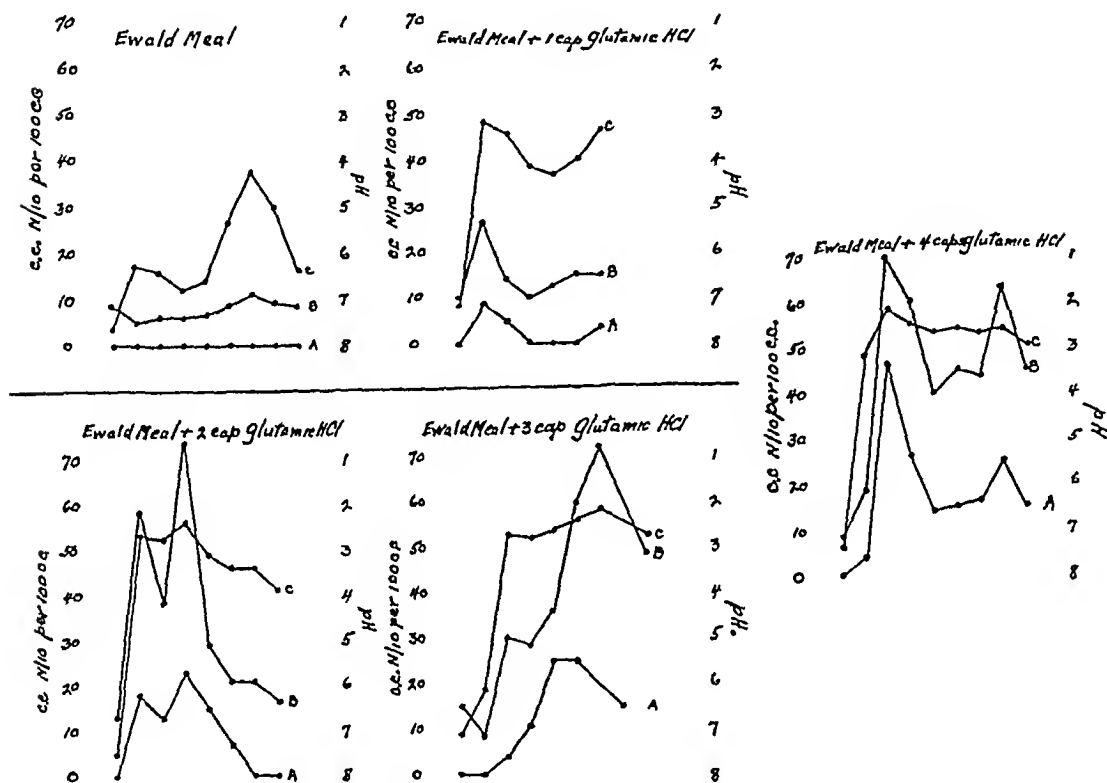


CHART 8 A = curve of free HCl B = curve of total acidity C = curve of pH

GLUTAMIC ACID HYDROCHLORIDE

Glutamic acid (α -amino-glutamic acid) was isolated by Ritthausen¹⁴ in 1869 from vegetable proteins by acid hydrolysis. It is very probably one of the essential amino acids, and in 1913 Abderhalden¹⁵ determined that it was a constituent of normal blood. Ikeda¹⁶ isolated the acid from a Japanese seaweed to which it gives its peculiar flavor. Moreover, in Japan it has for some time been used as a seasoning for foods, and in that country the use of the sodium salt—the most useful of the non-poisonous metallic radicals—has become widespread. Newbough and Marsh¹⁷ studying the toxic effects of amino acids established that doses of glutamic acid as large as two grams per kilogram body weight, when injected into rabbits and puppies, gave no evidence of renal injury. Tagawa¹⁸ considers glutamic acid a physiological protein decomposition product which, like meat extracts, has the ability strongly to stimulate hydrochloric acid secretion, while secre-

tion by the stomach is still possible. In the metabolism of glutamic acid, cognizance must be taken of the fact that three of its carbon atoms enter into the formation of glucose¹⁹. This, according to Ringer, Frankel and Jonas,²⁰ takes place by way of succinic acid.

Combined with hydrochloric acid to form a white powder, glutamic acid lends itself to easy administration in capsule form. Recently, von Bergmann²¹ recommended its use in an acidity, and Mahlei²² studied its effect, in the form of muirpsin (glutamic acid hydrochloride and pepsin), on both the gastric chemistry and on the appearance of the gastric mucosa through the gastroscope. Mahlei found that even in large dosage, it produced no hyperemia. We have done comparative studies with glutamic acid hydrochloride,* and with varying quantities of the official dilute hydrochloric acid. In contact with water, the combination is readily broken up, and the hydrochloric acid liberated. Considering that glutamic acid hydrochloride was one of the first amino acid salts to be isolated in pure form (Hlasiwetz and Habermann²³ in 1873), it is indeed surprising that it did not find its way much earlier into the replacement therapy of an acidity.

If we take the titration and hydrogen-ion concentration figures as seen in the charts 1 to 8 as a measure of the effectiveness of the replacement therapy in an acidity, the superiority of glutamic acid hydrochloride over the official dilute hydrochloric acid is obvious. With relatively small amounts of this combination, a close parallelism of the gastric acid curve in the achlorhydric with that which would be the response in the normal acid stomach to the usual Ewald test meal can be seen—a simulation not achieved even with enormous doses of the official hydrochloric acid solution.

At times we obtained titration figures, especially after the larger doses of the glutamic acid, which are normally never seen in the gastric juice. These were probably caused by a portion of the ingested drug which had not been mixed with the gastric contents. Charts 6, 7, and 8 also demonstrate the marked difference between free and total acid titration, following the use of glutamic acid hydrochloride. This is probably due to the glutamic acid content.

We have attempted to determine the approximate equivalent of the glutamic acid hydrochloride in terms of dilute hydrochloric acid both in vitro and in vivo. Table 1 represents the titration and pH figures of varying amounts of dilute hydrochloric acid, glutamic acid, and glutamic acid hydrochloride, each dissolved in 100 c c of distilled water. Titration was done to pH 7.4 using a comparator block and phenol red as indicator. Hydrogen-ion concentration was determined with the quinhydrone electrode. It will be noted that solutions of glutamic acid alone were included only up to three capsules (0.93 gr.), since that represented the degree of solubility of that acid in 100 c c of water.

In vitro experiments showed the titration figure of the contents of one

* Glutamic acid hydrochloride was kindly supplied by the Calco Chemical Company, Inc., for these investigations.

TABLE I

Dissolved in 100 c c distilled H ₂ O	Titration to pH 7.4 (c c N/10 per 100 c c)	pH
10 drops dil HCl (U S P)	16.3	1.85
1 cap glutamic acid	17.0	3.23
1 cap glutamic HCl	34.3	2.14
20 drops dil HCl	31.9	1.57
2 cap glutamic acid	34.1	3.20
2 cap glutamic HCl	68.7	1.92
30 drops dil HCl	46.1	1.41
3 cap glutamic acid	45.5	3.19
3 cap glutamic HCl	101.0	1.85
40 drops dil HCl	64.3	1.27
4 cap glutamic acid	Not completely soluble	
4 cap glutamic HCl	133.5	1.76
60 drops dil HCl	98.6	1.11
6 cap glutamic HCl	202.0	1.67
80 drops dil HCl	132.5	1.00
8 cap glutamic HCl	270.7	1.58

capsule of glutamic acid hydrochloride to be equivalent to about 20 drops of dilute hydrochloric acid, or equivalent to one capsule of glutamic acid (0.31 gm) plus 10 drops of dilute hydrochloric acid. The titration of larger amounts of the glutamic acid hydrochloride bear out this relationship. Yet in vivo the effectiveness of the glutamic acid hydrochloride in altering the intragastric reaction is far greater than its equivalent in vitro titration would indicate (charts 7 and 8).

If then the intragastric effects are to be considered a measure of the therapeutic efficiency, one capsule (0.31 g) of the glutamic acid hydrochloride appears to be as effective as a massive dose of the dilute hydrochloric acid. If to this greater ability to alter the gastric chemistry is added the ease of administration and the elimination of the unpleasant mouth effects of the official acid, we have in glutamic acid hydrochloride a highly desirable addition to the replacement therapy of anacidity. In one patient we noticed that considerable bladder irritation and frequency produced when adequate dosage of the official acid was administered to control a gastrogenous diarrhea were entirely relieved when glutamic acid hydrochloride was substituted. Clinically we have obtained satisfactory results from the administration of one capsule (0.31 g) of the glutamic acid hydrochloride shortly after the beginning of the meal, and another capsule at the completion of the meal.

SUMMARY AND CONCLUSIONS

The problem of anacidity has been subjected to rather one-sided investigation, and achlorhydria and its relation to duodenal function carries many implications which have thus far been overlooked. Gastric hydrochloric acid is the intrinsic agent which upon its arrival into the duodenum

originates the production or liberation of a group of hormones that have far-reaching physiological effects, and this gives to replacement therapy a greater significance than the mere relief of vague digestive symptoms or of a gastrogenous diarrhea. The inadequacy of the official dilute hydrochloric acid, even in massive doses, to alter gastric chemistry is illustrated by fractional gastric analyses, both by acid titration and hydrogen-ion determinations. The marked superiority of glutamic acid hydrochloride in relatively small dosage over the dilute hydrochloric acid is similarly demonstrated, as well as its advantages in administration.

In all, 104 gastric studies were made on 14 cases of achlorhydria, nine of whom had shown no response to histamine injection. The charts used for illustrations were selected from this group.

BIBLIOGRAPHY

- 1 CASTLE, W. B., HEATH, C. W., and STRAUSS, M. B. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. IV. A biologic assay of the gastric secretion of patients with pernicious anemia having free hydrochloric acid and that of patients without anemia or with hypochromic anemia having no free hydrochloric acid and of the role of intestinal permeability to hemopoietic substances in pernicious anemia, *Am Jr Med Sci*, 1931, clxviii, 741.
- 2 BAYLISS, W. M., and STARLING, E. H. The mechanism of pancreatic secretion, *Jr Physiol*, 1902, xxviii, 325.
- 3 FREUD, J., and SAADI-NAZIM. Action des injections intra-duodenales d'acide sur la secretion interne du pancreas, *Compt-rend Soc de biol*, 1926, xc, 571.
- 4 IVY, A. C. Factors concerned in the evacuation of the gall-bladder, *Medicine*, 1932, vi, 345.
- 5 SHAY, H., and GERSHON-COHEN, J. Experimental studies in gastric physiology in man. II. A study of pyloric control, the roles of acid and alkali, *Surg, Gynec and Obst*, 1934, lvi, 934.
- 6 SHAY, H., and GERSHON-COHEN, J. Experimental studies in gastric physiology in man. IV. The motor function of the resected stomach, *Am Jr Digest Dis and Nutr*, 1935, ii, 608.
- 7 FARRELL, J. I., and IVY, A. C. Studies on the motility of the transplanted gastric pouch, *Am Jr Physiol*, 1926, lxxvi, 227.
- 8 LIM, R. K. S., LOO, C. T., and LIU, A. C. Observations on the secretion of the transplanted stomach, *Chinese Jr Physiol*, 1927, i, 51.
- 9 (a) QUIGLEY, J. P., ZETZLEMAN, H. J., and IVY, A. C. Analysis of the factors involved in gastric motor inhibition by fats, *Am Jr Physiol*, 1934, cxiii, 643.
(b) QUIGLEY, J. P., and PHELPS, K. R. The mechanism of gastric motor inhibition from ingested carbohydrates, *Am Jr Physiol*, 1934, cx, 133.
- 10 IVY, A. C. In Discussion at Meeting of American Gastroenterological Association in June, 1935, to be published in *American Journal of Digestive Diseases and Nutrition*.
- 11 HURST, A. F. Achlorhydria: its relation to pernicious anemia and other diseases, *Lancet*, 1923, i, 111.
- 12 CROHN, B. B. Studies in fractional estimation of stomach contents. III. Effects of hydrochloric acid therapy on the acid titer of the stomach during digestion, *Am Jr Med Sci*, 1918, clvi, 656.
- 13 KERN, R. A., ROSE, E., and AUSTIN, J. H. Effect of orally administered hydrochloric acid upon gastric contents in normal individuals and in patients with achlorhydria, *Jr Clin Invest*, 1926, ii, 545.

- 14 RITTHAUSIN, H Aspiraginsäure und Glutaminsäure, Zersetzungsprodukte des Legumins und Conglutins beim Kochen mit Schwefelsäure, *Jr f prakt Chem*, 1869, cxi, 218
- 15 ABDERRHAJIDIN, E Der Nachweis von freien Aminosäuren im Blute unter normalen Verhältnissen, *Ztschr f physiol Chem*, 1913, lxxviii, 478
- 16 IKEDA, K On the taste of the salts of glutamic acid, *Eighth International Congress of Applied Chemistry*, 1912, viii, 147
- 17 NEWBURGH, L H, and MARSH, P L Renal injuries by amino acids, *Arch Int Med*, 1925, xxxvi, 682
- 18 TACAWA, J Über die Magensekretionserregende Wirkung der Salzsäuren Aminosäuren, *Biochem Ztschr*, 1931, ccxliii, 330
- 19 Lusk, G The production of sugar from glutamic acid ingested in phlorhizin glycosuria, *Am Jr Physiol*, 1908, xxi, 174
- 20 RINGER, A I, FRANKEL, E M, and JONAS, L The chemistry of gluconeogenesis IV The fate of succinic, malic and malonic acids in the diabetic organism, with consideration of the intermediary metabolism of aspartic and glutamic acids, proline, lysine, arginine and ornithine, *Jr Biol Chem*, 1913, xiv, 541
- 21 VON BERGMANN, G Die Bedeutung der Anazidität des Magens und einer Ausreichenden Substitutionstherapie, *Deutsch med Wchnschr*, 1933, lix, 1, 44
- 22 MAHLER, P Über die Beeinflussung der Magensaftsekretion durch kombinierte Salzsäure und Glutaminsäuretherapie, *Med Klin*, 1933, xxx, 943
- 23 Quoted by Mahler ²²

THE MEDICAL AND ECONOMIC ADVANTAGES OF ROENTGENOGRAPHIC CHEST SURVEY OF ALL HOSPITAL ADMISSIONS¹

By FRED JENNER HODGES, M D , *Ann Arbor, Michigan*

FEW radiographic procedures lend themselves more readily to routine mass application than simple postero-anterior filming of the chest. Other than removal of clothing above the waist-line no advance preparation of the patient is necessary. Great speed without sacrifice of quality can be attained in handling patients because positioning is simple and exposure time is measured in split seconds. Photographic processing in volume offers no serious problem.

Roentgenographic examination of the chest provides a wealth of detailed information concerning the thorax and its contents unrivaled by any other method of approach. The finished film serves furthermore as a valuable objective record which may be preserved for future reference. Even those roentgenograms presenting no recognizable abnormality become valuable as controls against which later chest changes may be contrasted. The predominance of requests for roentgen-ray consultations in which chest examination is required among all of the numerous procedures employed by the roentgenologist bespeaks the soundness of this contention.

It is by no means an uncommon experience to find roentgen-ray evidence of extensive pulmonary or mediastinal disease in the face of negative or inconclusive physical findings. Such findings, furthermore, may be associated with no suggestive symptoms. Purely upon the basis of such reasoning there seems to be no valid reason for withholding the benefits to be derived from this simple procedure from any patient seeking medical advice.

There is one possible reason, however, the validity of which need scarcely be urged, namely, prohibitive cost, cost not only to the person who must pay the material roentgen-ray expense as well as the professional fee for interpretation but, in addition, the initial investment cost to the hospital, clinic, or private practitioner of roentgenology. In order to test the actual value of routine roentgen-ray chest survey and to determine whether or not the cost need necessarily prove prohibitive, all patients registering in the University Clinic, both the hospital and out-patient groups, during the period from June 27 to July 13, 1935 inclusive, were so examined. It was recognized in advance that there could be no prospect of a permanent institution of the plan unless it could be shown that it could justify itself amply in the matter of medical value and at the same time prove itself to be self-supporting without imposing financial hardship upon registering patients. Before

* Read before the Fifth General Session of the American College of Physicians, Detroit, March 4, 1936.

From the Department of Roentgenology, University of Michigan, Ann Arbor, Michigan

the test was begun it was decided that unless the following benefits could be demonstrated the plan could not hope to become permanent

- 1 Increased diagnostic accuracy
- 2 Increased diagnostic speed
- 3 Economy for the patient (lowered aggregate roentgen-ray cost to group)
- 4 Economy for the institution (increased speed in clearing patients, no loss of revenue in Department of Roentgenology)
- 5 Increased availability of roentgenological service to entire patient group by spread of cost

PHYSICAL FACILITIES AND METHOD OF PROCEDURE

In order that patients might be examined with greatest possible dispatch and the minimum inconvenience, apparatus was set up in a small room 12' by 12', immediately adjoining the room in the registration department where blood samples are routinely taken for serological examination. Seven temporary dressing rooms were erected in the corridor as well as a small, light-proof film loading room. To insure roentgenograms comparable to those made with the regular chest apparatus in the roentgen-ray department, a machine was installed capable of producing satisfactory exposures at six foot distance in 1/50 second. High speed of exposure furthermore eliminated the necessity for rigid fixation of the patient. A technician was provided throughout registration hours as well as a ward helper to attend patients. Stock celluloid films of 14 by 17 size were used rather than less costly paper, again in order to maintain uniformity of roentgenographic quality as well as to permit photographic processing with existing facilities. All films were developed during the night by a second technician employed for that purpose to avoid crowding in the roentgen-ray dark room. All films were identified photographically with date and a serial number which last was entered upon a card bearing a duplicate imprint of the patient's admission data. When processed, all films were stored for three months, unread, in order that the immediate results of the test might not alter the regular handling of the patient and to permit ultimate disposal of the cases without bias. At the end of the three month period all films were read in unbroken sequence by the assembled staff of the Roentgenology Department. Diagnostic statements were recorded in accordance with a prearranged code designed to permit direct transfer to punch cards for mechanical sorting (table 1). In addition to diagnostic material, such information as age, sex, race, service to which admitted, registration number, and home county were also recorded on the cards. Similar punch cards in the main record room, accessible by registration number, were already available carrying complete information regarding clinical diagnosis, type of treatment, and disposition of the case. Roentgen-Ray Department records were available in similar form permitting correlation between survey film diagnosis and any subse-

TABLE I

Classification of diagnoses made from survey films

- A Frank negative admission roentgenogram
- B Positive admission roentgenogram which may or may not be clinically significant
 - 1 Anomalies of ribs
 - 2 Other bony change, ribs or spine
 - 3 Abnormal aorta
 - 4 Pleural changes apex, axilla, diaphragm, costophrenic angle
 - 5 Calcification pleura, lymph nodes, parenchyma
- C Positive admission roentgenogram, clinically significant
 - 1 Abnormality, thyroid or mediastinum
 - 2 Abnormal cardiac size or shape
 - 3 Non-tuberculous pulmonary disease
 - 4 Pleural effusion
 - 5 Intrathoracic glandular tuberculosis
 - 6 Parenchymal tuberculosis

quent roentgenologic opinions which had been rendered. The total expense of the test was borne by the Department of Roentgenology as an investigative project. Patients were submitted to subsequent roentgen examination only at the express desire of the clinic staff and for reasons they deemed sound. Neither the economic limitations nor the medical indications of roentgen-ray examination were disturbed.

RESULTS

During the 11 full working days and three half days of the test period a total of 1,116 newly admitted patients were subjected to chest survey examination. Every person passing through the blood-sampling room was so examined. Persons admitted directly to the hospital as emergency patients were not included. The films in 15 instances were for one reason or another unsatisfactory, leaving a total of 1,101 chest films representing a like number of individuals.

The various situations listed in the diagnostic code employed (table 1) are shown in table 2 grouped under the three main subdivisions A, normal, B, changes of questionable importance, and C, clinically significant situations.

TABLE II

Service	No Pts	Class A	Class B	Class C
Unidentified	1		1	
Obstetrics	14	8	6	
Oral Surgery	28	21	5	2
Urology	33	19	18	6
Neurology	60	41	15	4
Ophthalmology	70	48	18	4
Otology	73	43	22	8
Gynecology	75	54	19	2
Dermatology	83	55	24	4
Bone and Joint	89	63	23	3
Surgery	113	73	24	16
Pediatrics	184	164	15	5
Medicine	278	162	80	36
Total	1101	751 (68.3%)	260 (23.6%)	90 (8.1%)

As was to be expected, the majority of the patients examined showed no roentgen evidence of chest abnormality. Group B, those in which non-significant deviations from the normal were observed, is interesting, but one can scarcely justify wholesale roentgen-ray examination on the basis of such returns. It is with the 81 per cent, which showed unequivocal changes usually indicative of significant disease, that our chief interest lies.

These 90 individuals had been filtered out of the entire series as persons harboring thoracic situations of prime medical importance. The yield may at first glance appear small, yet when it is remembered that these 90 patients came to the clinic for all manner of situations, it will be recognized that in many instances the discovery of the chest lesion was often times scarcely to be expected on the basis of symptomatology. As a matter of fact, 50 of these 90 patients were cleared through the clinic without being referred to roentgenology, and in but 15 of that 50 was the chest situation, demonstrated by the survey film, diagnosed on the basis of physical findings. This leaves 35 patients in whom chest changes, presumably clinically significant, were observed in survey roentgenograms upon admission whose later study without roentgen examination failed to reveal intrathoracic disease. Careful review of all available data in this selected group of cases showed that in 10 instances the originally observed abnormalities were perhaps open to some question, that in seven instances the abnormality consisted of cardiac enlargement only, while in four instances the probable clinical significance of the observed changes might well be questioned. This process of elimination left a very significant group of 14 patients, representing 15.5 per cent of the entire "C" group, or 1.5 per cent of the entire test series, which must be considered as diagnostic failures in so far as chest status is concerned. These 14 cases deserve individual consideration. Four of these cases showed evidence of pneumonitis of unspecified character.

Case 1 E P, f, aged 40. Admitted 7-5-35 to Otolaryngology
Survey film. Pneumonic infiltration, right median base
Clinical diagnosis. Previous thyroidectomy and tracheotomy. Vocal cord palsy
Discharged 7-17-35
No re-admission

Case 2 E M, m, aged 59. Admitted 6-27-35 to Neurology
Survey film. Pneumonitis, right base
Clinical diagnosis. 1. Left hemiplegia
2. Latent lues
3. Borderline heart size
4. Arteriosclerosis
Discharged 6-27-35
No re-admission

Case 3 I M, f, aged 55. Admitted 7-12-35 to Dermatology
Survey film. Pneumonitis
Clinical diagnosis. Rodent ulcer, recurrence
Discharged 7-12-35
No re-admission

Case 4 S B , f , aged 7 Admitted 7-2-35 to Pediatrics

Survey film Pneumonitis, right base

Clinical diagnosis 1 Strabismus
2 Tenia saginata

Discharged 7-2-35

No re-admission

The roentgen-ray findings in all of these represent disease which may yet manifest itself by serious clinical symptoms and may well prove to be of serious importance

Five of the group presented roentgen signs of tuberculosis



FIG 1 Minimal pulmonary tuberculosis, left apex

Case 5 M T , f , aged 17 Admitted 7-12-35 to Orthopedic Surgery
Survey film Minimal pulmonary tuberculosis, left apex (figure 1)
Clinical diagnosis Healed chronic osteomyelitis, right femur
Discharged 7-12-35 (same day)
No re-admission

Case 6 J K , m , aged 42 Admitted 7-10-35 to Internal Medicine
Survey film Minimal pulmonary tuberculosis
Clinical diagnosis Questionable chronic ulcerative colitis
Discharged 7-16-35
No re-admission

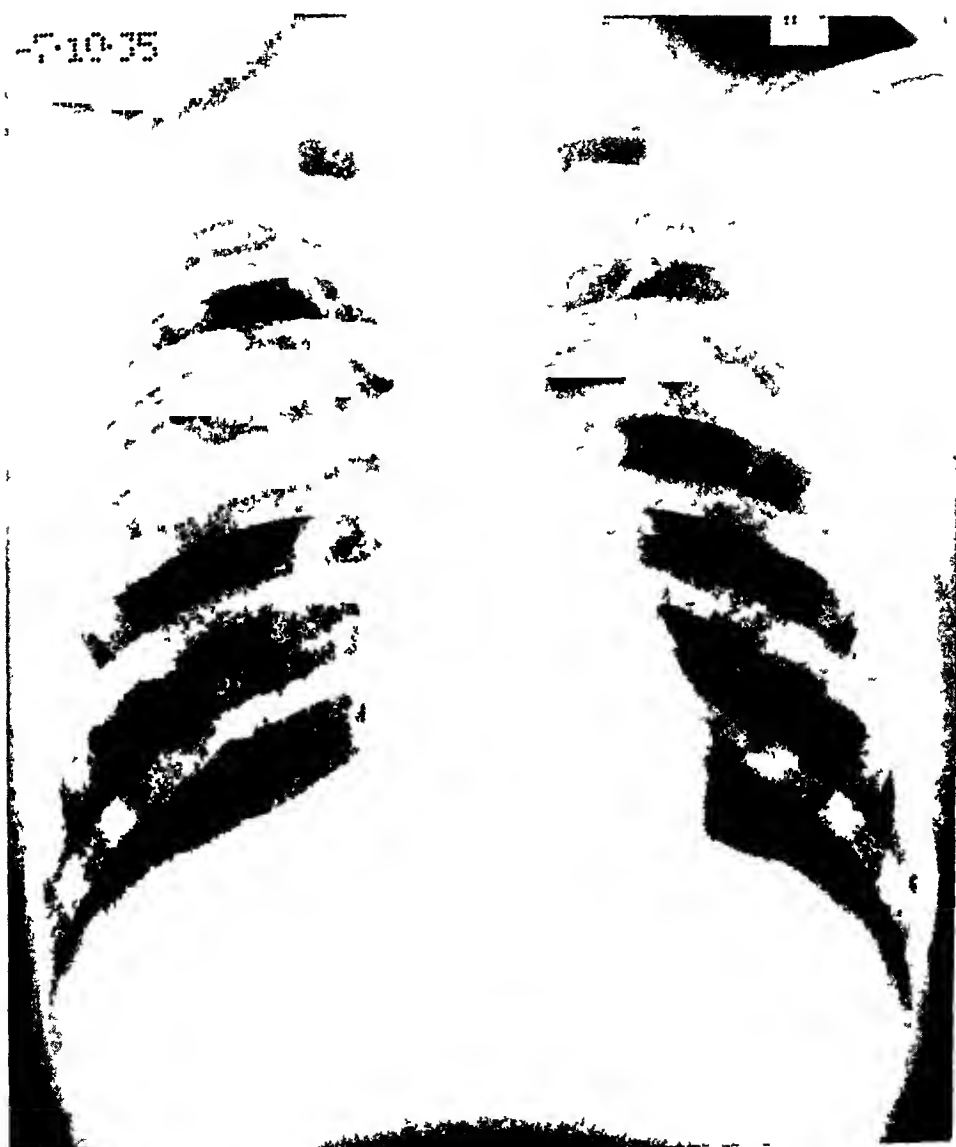


FIG 2 Minimal pulmonary tuberculosis, right apex

Case 7 C M , m , aged 26 Admitted 7-10-35 to Oral Surgery
Survey film Minimal pulmonary tuberculosis right apex (figure 2)
Clinical diagnosis Abscessed tooth (tooth extraction)
Discharged 7-10-35 (same day)

No re-admission Record at University Student Health Service 2-28-36 reveals tuberculosis recognized July 1933 No such information on University Hospital record

Case 8 G B , m aged 52 Admitted 7-8-35 to Internal Medicine
Survey film Minimal pulmonary tuberculosis
Clinical diagnosis Gastritis
Discharged 7-10-35
No re-admission

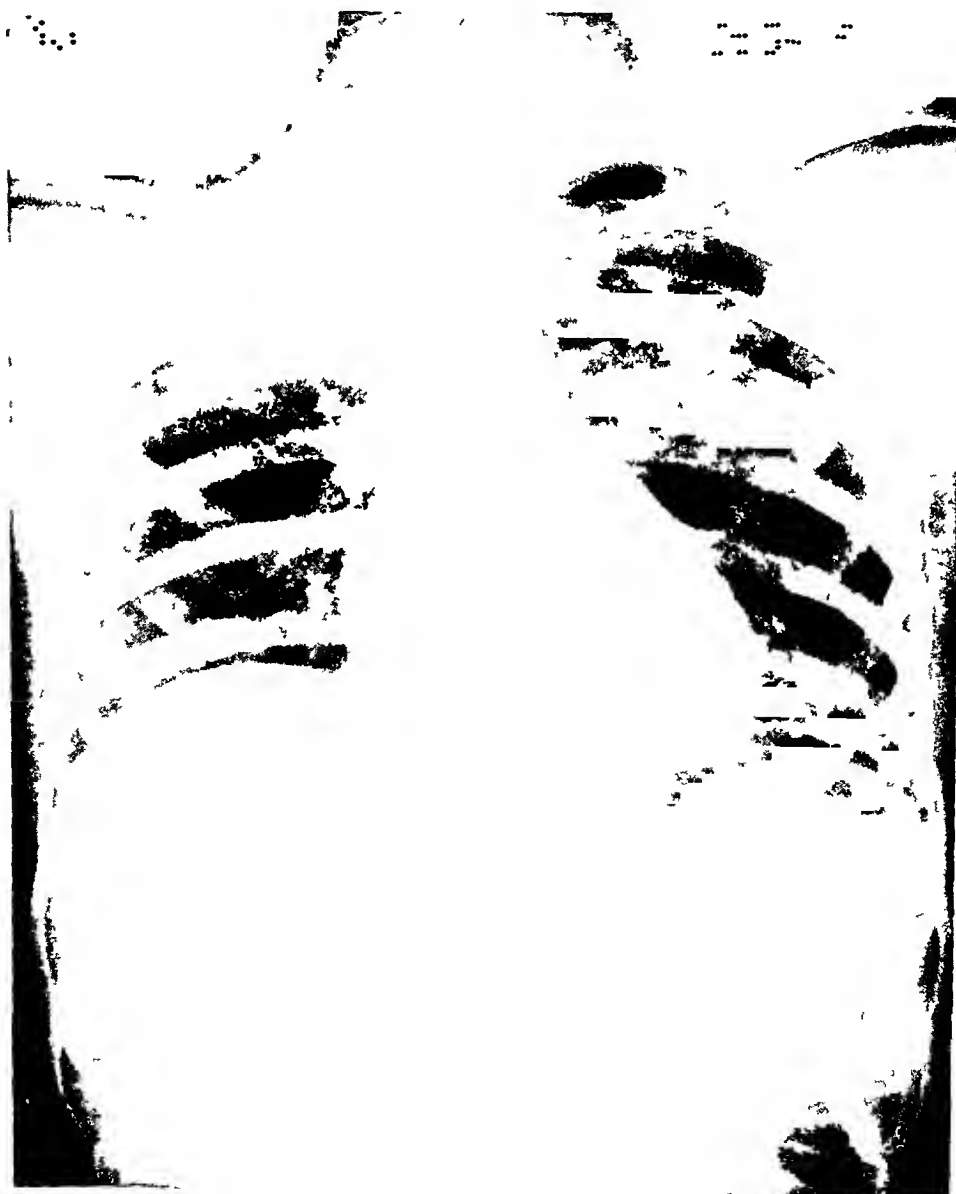


FIG 3 Tuberculous pneumonia, right upper lobe

Case 9 A M , f , aged 12 Admitted 7-2-35 to Pediatrics
 Survey film Tuberculous pneumonia, right upper lobe (figure 3)
 Clinical diagnosis Septic tonsils and adenoids
 Tonsillectomy
 Adenoidectomy
 Biopsy Negative for tuberculosis of tonsils
 Discharged 7-9-35
 No re-admission



FIG 4 Substernal thyroid enlargement and metastatic pulmonary lesion, right apex

In all of these cases, tuberculosis if recognized would surely have been subject to careful clinical evaluation and treatment

Case 10 O D , m , aged 19 Admitted 7-1-35 to Orthopedic Surgery
 Survey film Apparent dextro-cardia
 Clinical diagnosis Idiopathic scoliosis
 Discharged 8-5-35
 Re-admission

Without further study the exact cardiac status can scarcely be determined from the single exposure

Four cases showed evidence of neoplastic metastasis to the lung

Case 11 F D , m , aged 68 Admitted 7-1-35 to Neurology

Survey film 1 Enlarged thyroid

2 Metastatic pulmonary lesion, right apex (figure 4)

Clinical diagnosis 1 Cerebral arteriosclerosis—paranoia

2 Arteriosclerotic heart disease

Discharged 7-3-35

No re-admission



FIG 5 Metastatic pulmonary lesions

Case 12 R H , m , aged 35 Admitted 7-2-35 to Otolaryngology

Survey film Metastatic pulmonary lesions (figure 5)

Clinical diagnosis Tubo-tympanitis

Discharged 7-2-35

No re-admission

Case 13 M G, f, aged 65 Admitted 6-27-35 to Gynecology
Survey film Multiple neoplastic metastases to lungs (figure 6)
Clinical diagnosis Undifferentiated medullary carcinoma, uterus
Roentgen therapy 7-5-35 to 7-9-35, 650 r 200 KV, to each of four pelvic ports
Clinical note 8-2-35—"Patient failing"—no further treatment advised
Death 8-11-35 No autopsy

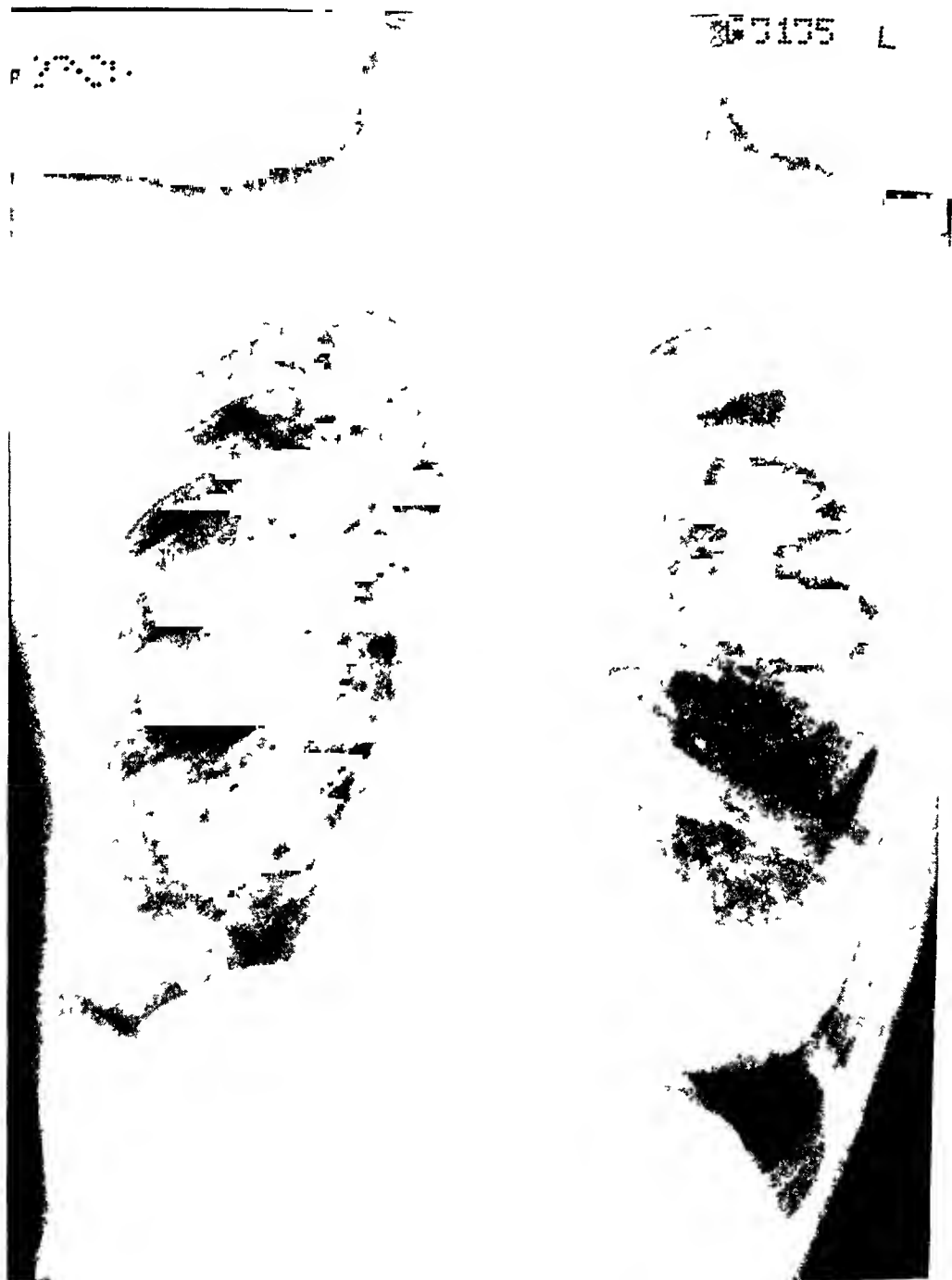


FIG 6 Multiple neoplastic metastases to lungs

Case 14 R W , m , aged 67 Admitted 7-1-35 to Urology
 Survey film Discrete pulmonary lesion Neoplastic metastasis or primary tuberculous lesion
 Clinical diagnosis Chronic prostatitis and epididymitis
 Discharged 7-1-35
 No re-admission
 (Unquestionably the handling of these patients would have been altered in the light of positive knowledge of metastasis)

These 14 instances of overlooked intra-thoracic lesion taken from the total admissions of 14 successive days indicate that we may expect one such oversight as a daily occurrence in spite of the care with which patients are examined The correction of this situation is of importance not alone to the individual patient in terms of future well-being, but also to the institution and its staff in protecting its reputation for diagnostic accuracy If insurance against daily errors in diagnosis can be purchased without excessive cost neither physician nor patient can afford to be without its protection

Considering the 40 cases of the "C" group in which accurate diagnosis was later achieved through roentgen information derived from examinations conducted at the request of the clinical staff, one finds that in several instances costly time was lost which would have been saved had the reports of the survey films been made immediately available This delay amounted to only two days in 29 instances, while in 11 cases 4 to 90 days elapsed before diagnosis was made from roentgen evidence The average time loss per patient for this group of 40 people was 6.75 days, representing a very real though unnecessary financial load

Four cases in particular from this group deserve specific mention

1 R H , f Admitted 7-2-35 to Gynecology
 Survey film Minimal pulmonary tuberculosis
 Clinical diagnosis Chronic pelvic inflammation No response to conservative treatment

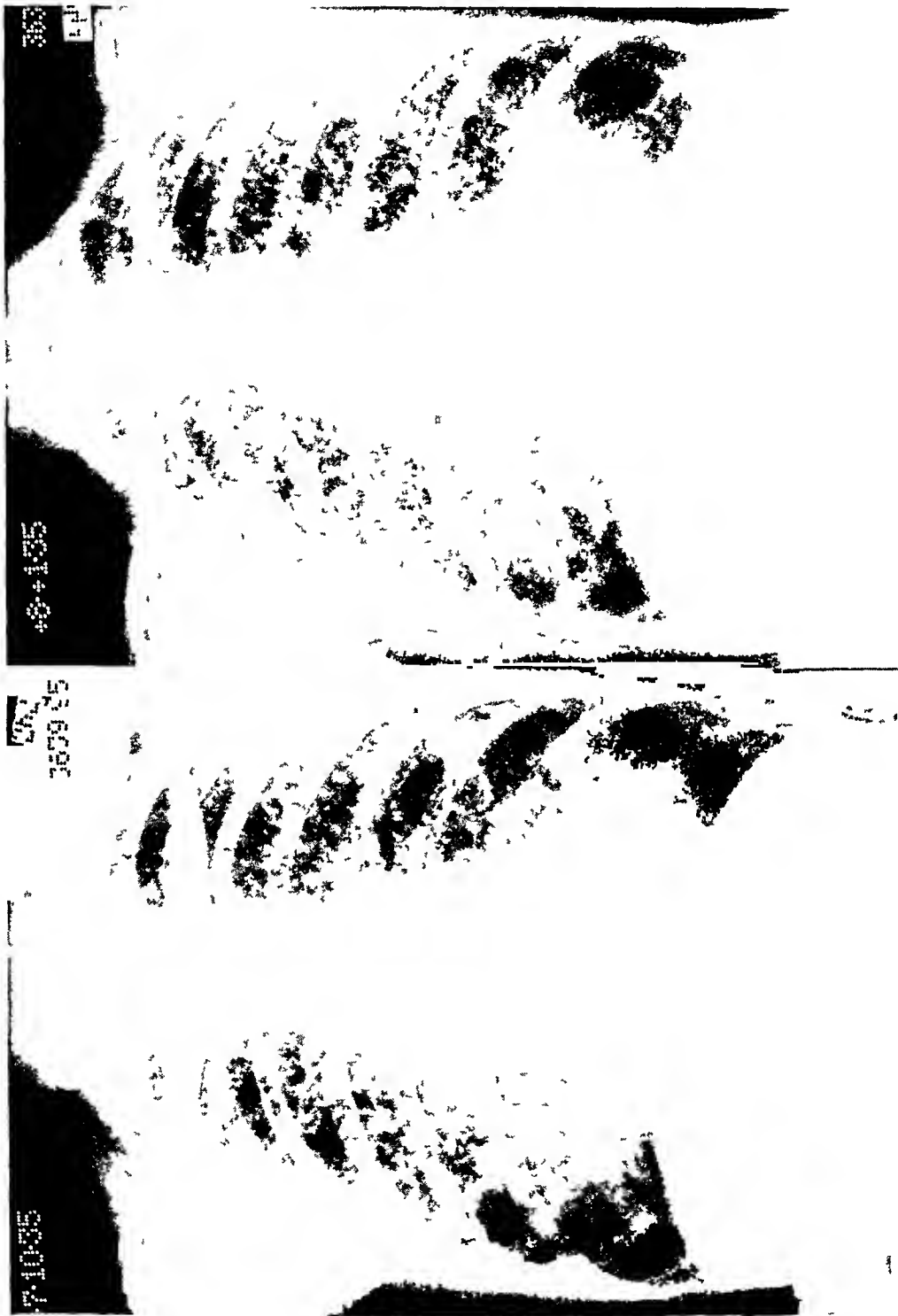
Roentgen-ray consultation 8-15-35 Minimal pulmonary tuberculosis
 (Still under treatment 3-1-36)

It is true that the course of treatment was not altered in this case

2 A T , f , aged 65 Admitted 7-10-35 to Dermatology
 Survey film Disseminated pulmonary tuberculosis (figure 7)
 Clinical diagnosis Pyogenic ulcer of scalp
 Roentgen examination of skull Luetic osteitis suggested
 Roentgen-ray consultation, chest, 8-1-35 Disseminated pulmonary tuberculosis
 Death 9-1-35
 Autopsy 9-2-35 Miliary tuberculosis lungs, spleen, liver, peritoneum, and left kidney Tuberculosis of scalp and skull

The generalized nature of the disease was unsuspected for 22 days

3 M S , f , aged 60 Admitted 7-8-35 to Medicine
 Survey film Neoplastic metastases right base (figure 8)
 Clinical diagnosis Carcinoma of colon
 Transferred to Surgery Cecostomy, 7-10-35



a

b

FIG 7 Disseminated pulmonary tuberculosis



FIG 8 (a) Neoplastic metastases, right base (b) Bedside film reported as postoperative pneumonia (respiratory movement resulted in blurring of sharply defined border of lesion)



FIG 9 (a) Large metastatic lesion, left upper lobe (Admission survey film) (b) Same case examined on direct refer 11 days later



FIG 10 (a) Reduction in size of metastatic lesion following roentgen therapy (b) Continued growth of metastatic lesion despite further irradiation

Roentgen-ray consultation (7-16-35 and 7-18-35) bedside chest examination
Postoperative pneumonia (respiratory movement resulted in blurring of sharply defined border of lesion)

Biopsy via sigmoidoscope 7-27-35 Adenocarcinoma

Discharged 8-9-35

Nineteen days earlier the nature and prognosis of this case could have been determined

4 M N , m , aged 29 Admitted 7-5-35 to Genito-urinary Surgery

Survey film Large metastatic lesion left upper lobe (figure 9 a)

Clinical diagnosis Teratoma of testis

Roentgen-ray consultation 7-16-35 Neoplastic metastasis, left lung (figure 9 b)

Roentgen therapy, 7-16-35 to 7-26-35, 1500 r, 200 KV, to scrotum, 600 r, 200 KV, to each of 10 chest and pelvic ports

Surgery 8-6-35 Removal of testicle

Biopsy 8-6-35 Chorioepithelioma

Roentgen-ray consultation, 8-6-35 Marked reduction in size of chest lesion (figure 10 a)

Roentgen therapy 8-28-35 to 9-10-35 400 r, 200 KV, to each of 10 ports

Roentgen-ray consultation, 1-3-36 Chest lesion enlarging

Roentgen therapy 1-7-36 to 1-8-36 600 r, 200 KV, to each of 2 chest ports

Roentgen-ray consultation, 2-19-36 Further increase in size of chest lesion

A delay of 11 days awaiting result of Aschheim-Zondek test before metastasis was recognized and radiation therapy instituted

COST OF SURVEY

Looking into the all important matter of costs of the venture several very interesting facts have come to light The actual material cost of producing single exposure chest roentgenograms on transparent film by the routine survey plan already outlined is surprisingly low even when one takes into account all items fairly chargeable against the project

TABLE III

Material or Non-Professional Cost of Survey

Capital cost	\$50 00*
40 gallons of developer @ 45¢	18 00
40 gallons of fixing solution @ 20¢	8 00
Technician 14 days @ 35¢ per hour	39 20
Ward-helper 14 days @ 33¢ per hour	36 96
Dark room labor 4 hours daily, 14 days @ 50¢ per hour	28 00
Stenographic service 32 5 hours @ 50¢ per hour	16 25
1116 14 by 17 films	558 89
	<hr/>
	\$755 30

* Note This figure represents a total capital investment for chest radiographic apparatus \$5000 00 plus \$1000 00 for necessary building alterations with interest at 6 per cent amortized over a five year period which is customary in this institution

It is our intention, if and when the chest survey plan becomes a permanent feature in this institution, to use transparent celluloid film cut to the special size of 13 by 14 inches This will mean narrowing the film by one inch and shortening the film by three inches which in the majority of cases will permit

inclusion of the entire thorax. For unusually large patients, 14 by 17 films can still be used, and conversely for small children 11 by 14 or even smaller films can be used. Since film costs vary directly with film area this will permit a still further reduction in the material cost of this type of examination. In fact, had the 13 by 14 size been used in this particular test the saving would have amounted to \$168.29. This additional saving will more than cover the customary 25 per cent charged against all budget expenditures in this institution for general administration overhead.

At this point it should be emphasized that over and above the preparation of satisfactory roentgenograms at material costs such as those already enumerated, the examination of such films by physicians trained in their interpretation is all-important if a survey of this sort is to have any medical value whatever. It goes without saying that this medical service entails further expense which can by no means be overlooked. By well established precedent throughout all branches of medicine the right to establish a suitable fee for his own personal services has long been reserved to the physician himself. It is not the intention of this communication to suggest what a proper fee for this medical service should be, but rather to point out that established roentgen laboratories whether privately owned or operated by hospitals or clinics, can render an exceedingly valuable service to referring physicians at a cost which need not be prohibitive. It will be remembered that the plan calls for a simple survey of the chest of *all* new admissions in order to quickly uncover unsuspected manifestations of disease within the thorax, to provide a record of that patient's chest for future reference and to direct both the roentgenologist and the referring physician in the matter of requesting and carrying out further, more detailed studies in those cases where further study seems advisable. It must not be inferred that present fees for individual stereoscopic examination of the chest or other special procedures are necessarily exorbitant. The reporting of survey films by mere indication as to whether the chest appears to be barren of pathological changes, shows evidence of changes which though interesting may not be significant, or shows definite evidence of abnormality requiring further study, is not time consuming and, if done in quantity, is not costly from the material viewpoint nor need it be costly from the professional viewpoint.

SUMMARY

To test the theory that it would be profitable to subject all persons presenting themselves for physical examination and treatment to a preliminary roentgenographic survey of the chest, this sort of examination was conducted on all patients registering at the University Hospital for a period of 14 successive clinic days. At the outset it was postulated that five conditions must be met if the plan were to be considered practicable. The first of these conditions, "increased diagnostic accuracy," was adequately met by the final results for a conservative estimate shows that in the group of

patients so studied 14 were found to present significant, if not alarming, chest situations which were not discovered by other means

The demand that the survey plan must demonstrate the ability to "increase diagnostic speed" was well shown by the fact that patients with significant chest changes, ultimately satisfactorily diagnosed, could have had these diagnoses pronounced on the average of 6.75 days sooner

It was postulated that the plan should constitute "no added financial burden to patients," that the aggregate roentgen-ray cost to the group of patients so examined did not exceed the amount paid by those few who by one method of selection or another might be sent for roentgenological examination of the chest in the ordinary course of events. Actually, of the total group surveyed numbering 1116 individuals, 164 patients were referred in for chest examination, the results of the admission survey having been withheld. These individuals actually paid in the aggregate \$99.00 more than the material cost of surveying the entire group. It is further true that the total survey cost did not include professional fee for interpretation. If one is willing to offset this additional cost to the patient group by the indeterminate saving, certainly to be affected by the reduction in time of complete examination set forth in the preceding paragraph, it may be assumed that no additional cost would have been imposed upon the patient group.

It is impossible to determine accurately the extent of any possible loss in revenue in the Roentgen-Ray Department which the fourth postulate insisted must not occur. It seems logical to assume that the 50 patients shown to have definite pathological changes in the chest, who were not subsequently subjected to roentgen examination at the request of the examining physician, would have been studied more thoroughly had the survey findings been known. Though the Department of Roentgenology would undoubtedly lose certain chest examinations done more or less on suspicion by the referring physician, it would at the same time gain more interesting and more extensive work as the result of the discovery of unsuspected chest lesions in the survey process.

The fifth and last condition to be met, namely, that roentgenological service presumably valuable might be extended to all patients by spreading costs has undoubtedly been satisfactorily shown to be true. Many of the benefits to be derived from a survey of this sort are not at first glance recognizable. Months, even years after the patient's original admission subsequently developing chest lesions may be compared in so far as their roentgen appearance is concerned with that same chest as it appeared on the date of first admission.

CONCLUSIONS

- 1 The methodical practice of submitting all patients presenting themselves to a hospital or clinic for physical examination to routine roentgenographic examination of the chest can be accomplished expeditiously and without great inconvenience to the patient.

2 Roentgenographic chest survey of all hospital and clinic admissions assists the examining physician in quickly determining which patients may profitably be subjected to more searching examination by the roentgen method

3 Routine chest survey may be expected to disclose alarming chest changes in approximately 8 per cent of patients presenting themselves to a general hospital or clinic

4 Significant chest disease unrecognizable by other methods and often totally unexpected on the basis of chief complaint and history may be expected in something over 1 per cent of large, diversified patient groups

5 Roentgenographic chest survey offers a means of increasing the speed with which obscure chest situations may be accurately diagnosed

6 The cost of offering this one type of roentgenographic service to all patients need not constitute an unwarranted financial burden upon patients

CHRONIC ARTHRITIS, A GENERAL DISEASE REQUIRING INDIVIDUALIZED TREATMENT *

By ERNEST E. IRONS, F A C P, *Chicago, Illinois*

HUNDREDS of discussions and scores of books have been written about arthritis—and still they come, largely because this condition occasions more disability than any other disease in temperate climates, and its care presents a greater multitude of difficulties. In presuming to bring to you so age-worn a subject, I plead as excuse the request of your President, and the fact, expressed in my title, that in recent years there has come a great change in the general conception of the relation of disease of the joints to disease of the rest of the body. This altered viewpoint makes easier the understanding of the variable course and symptomatology of arthritis, and facilitates the formulation of a program of treatment suited to each patient. I can offer little that is new, but perhaps may present old observations in a relationship which will be serviceable in planning treatment.

Before passing to the problems of chronic arthritis it is of interest to recall that much acute arthritis is clearly related to infections, and occurs as a part of the general infectious process. Frequently the causative organism such as gonococcus, streptococcus or pneumococcus is demonstrable in cultures from the infected joints. The number of joints involved, however, is remarkably small when considered in relation to the number of times that bacteria must reach joint structures in the course of the demonstrated bacteremias of infectious diseases. Furthermore, the infected joints usually heal under appropriate treatment and rest, without residual impairment of function. We may conclude that the cartilage and other joint tissues of normal persons are fairly resistant to infectious insults.

This suggests that when joints fail to heal, and the arthritis passes into more chronic forms, factors other than the initial infection, such as inferior cartilage, impaired blood supply and nutrition, may be concerned in the disease.

Causes other than infection such as serum disease, hemorrhagic diseases, as well as trauma, may also initiate acute arthritis. The parallelism noted between the acute arthritic phenomena of serum disease and the exacerbations of arthritis in rheumatic fever can be readily extended to some of the acute exacerbations of chronic arthritis which follow acute respiratory infections.

The concept of chronic arthritis as a general disease, rather than one of the joints alone, is steadily gaining ground. It is generally conceded that there are many initiating and contributing causes of chronic arthritis. These include infection, trauma, the wear and tear of use, heredity, dis-

* Presented at the Detroit meeting of the American College of Physicians, March 2, 1936.

turbances of vascular supply or of general and local nutrition, metabolic and glandular dysfunction and the degenerative changes of advancing age. Various combinations of these causes and conditions in individual patients result in varying clinical pictures, whose common factor is involvement of joints and structures attached to the bony skeleton. No one single cause or condition is common to all cases of arthritis.

Many classifications of chronic arthritis have been suggested, but as so often happens the simplest seems the best, and the division of chronic arthritis into atrophic (rheumatoid) and hypertrophic (osteo-) arthritis, suggested by Garrod in 1890, and by others later, has been adopted by the American Committee. The British Committee suggests a classification, similar but somewhat more elaborate.

Atrophic (proliferative, rheumatoid) arthritis occurs in the younger age groups, often in women, and is characterized by multiple joint involvement with fusiform appearance of joints of fingers, often ulnar deflection, and later ankylosis. The onset is either insidious or acute, and evidence of initial and often of continuing infection is frequent. In many patients constitutional effects with slight fever, anemia, and poor nutrition are marked.

Hypertrophic arthritis begins on the average somewhat later, or beyond middle life, in persons often well-nourished, and causes disability from slight to severe crippling. It is usually polyarticular but may be monoarticular. Lipping of joints, and hyperostoses are frequent, ankylosis is rare. Fibrous thickenings, Heberden's nodes with later bony hyperplasia at the terminal joints of the fingers are common. The effects of the trauma of work are often noted in the hands and spine of the laborer. Evidences of infection are much less frequent than in the atrophic form and when discovered, their removal influences but little the course of the arthritis. Arthrosis, which has been suggested to replace the term arthritis of this type, has at least the virtue of being less committed to the inflammatory concept.

Certain difficulties are met with, however, in accepting the dictum that the two types are etiologically and clinically distinct diseases in the same sense that lobar pneumonia and typhoid fever are from the beginning, by reason of their etiology, different diseases.

Now and then joints in the same patient show in one the pathologic anatomy commonly found in atrophic arthritis and in another the pathologic changes of hypertrophic arthritis. While evidences of infection predominate in atrophic arthritis and are usually minimal in hypertrophic arthritis, there are exceptions in which acute inflammatory processes occur in the hypertrophic form. The Heberden nodes, frequently found in chronic hypertrophic arthritis, may at times become acutely tender, red, and swollen following acute (such as respiratory) infections. Trauma of work, a large factor in hypertrophic arthritis, also appears in evidence in atrophic arthritis in which the right hand in a right handed person shows more extensive change than the left.

The location of the affected joint and the degree of its exposure to the trauma of weight bearing have been shown to influence the type of arthritis which develops. The effect of heredity seems as clear in atrophic arthritis occurring in grandmother, mother and daughter as in the family incidence of early hypertension. Racial, familial and individual peculiarities in connective tissue response to injury, as illustrated by the variable formation of keloid in surgical scars, and the varying rapidity and extent of callus formation after fractures indicate the wide range of individual tissue response to trauma. The same factors undoubtedly influence the healing of tissues of joints.

Is it not possible that the disease process in chronic arthritis assumes this or that course with the production of one or another type of arthritis by reason of the kind, age and resistance of tissues of the patient whose joints have suffered an initial insult? It may even be argued that the same insult which initiates in one person an atrophic arthritis, might, if received by a person whose tissues were less vulnerable, have caused no more than a temporary disability. In this connection, consider the variety of types of arthritis which may follow gonococcal infection, from an acute temporary and quickly healing arthritis, to the chronic forms, indistinguishable from "atrophic arthritis" or again from spondylitis ankylopoietica of the British classification.

The predominance of infection in atrophic arthritis as compared to hypertrophic arthritis is evident, but the cause for this predominance may well lie in the poor resistance to infection of the patients' tissues in general, including those of the joints, which also in these cases are less well able to withstand injury and heal than are those of persons with a better heredity.

In this sense we may regard the person whose general resistance to infection is below the normal, and whose cartilage and joint tissues are by reason of heredity less able to withstand insults and to heal than are those of normal persons, as potentially a candidate for atrophic arthritis. In such a person, further lowering of resistance to infection, malnutrition, overwork, extreme nervous strain, as well as severe infections, especially those of the respiratory tract, become etiologic factors in the atrophic arthritis which follows. The arthritis which gives the clinical name to the condition is thus only one expression of the more fundamental general disease.

It is generally agreed that the division of chronic arthritis into two great groups, the atrophic (rheumatoid) and hypertrophic (osteo-) arthritis is extremely serviceable. One of the chief values of this classification rests on the fact that it takes into consideration the previous reactions of the tissues of the patient and so prophetically indicates the kind of changes he is likely to suffer in the future, and, therefore, the measures which should be taken to meet and modify the disability which threatens him.

Borderline cases, and those in which both types are found in the same patient, are accounted for by unusual combinations of causes including vary-

ing exposure to trauma, and the peculiar tissue reactions of the individual patient

With this multiplicity of continuing causes of chronic arthritis in mind, the original initiating cause, not infrequently undeterminable, becomes less important, and the care of the present problems of the patient moves to the fore

Again, we may ask, does the presence or absence of infection determine the course and type of the arthritis, or is infection present (either active, or apparently not participating in the progress of the disease) by reason of decreased general body resistance to infection, and not because of the presence of arthritis? If the latter, we may then conceive of atrophic arthritis as occurring in persons whose cartilage and joint structures heal less readily when injured than in the usual normal person, and whose resistance to infection is also below the normal. When such a person suffers from an infection his joints are less likely to escape, and once involved, healing is incomplete and the process becomes a progressive one. He is likely to suffer from recurrent infections especially streptococcal, with exacerbations of joint disease, and studies of his blood will show the evidences of infection

The process in the joints, which gives the name of arthritis to the illness, is subordinate to the more fundamental basic constitution of the patient, in respect to his general resistance to infection and to the ability of his joint tissues to heal or to resist varying degrees of trauma. Again the emphasis falls on the general features of disease in the body rather than on that in the joints alone. In the established case of hypertrophic arthritis, infection seems to play but a minor part, nutrition suffers little, there are degenerative changes in cartilage and much of the disability results from marginal ossification, and mechanical interference with joint motion

TREATMENT

Clinical experience and methods of treatment of chronic arthritis have progressed through the study of the effects of treatment of groups of patients by one or another method, such as the search for and removal of infections, the giving of this or that drug, attempts at immunization by vaccines, the use of special diets or the employment of physical therapy. These surveys have required enormous expenditure of effort, and an industry that commands admiration. Some of these studies have been well controlled and have taken into consideration the natural history of arthritis and its well recognized tendency to spontaneous remissions. Others have consisted of uncritical observation of many patients for short periods, and are of little or no value

Some patients have been benefited by each of the remedies exhibited but, as might be anticipated, no one remedy has proved to be curative in a large proportion of groups of patients so selected

No two patients present the same combination of symptoms nor are

their problems to be met in exactly the same manner. Different combinations of causes may result in arthritis of essentially the same type, although certain causes undoubtedly tend to be associated with one or the other type. The type of arthritis which will develop depends on the age, nutrition and kind of tissues of the patient.

For purposes of a general survey and classification of arthritis, the study of patients in large groups is necessary, but for purposes of treatment and cure the unit of study is the individual patient. In chronic arthritis, as in the solution of current economic problems in medicine, methods of mass production are bound to fail.

There are certain general and special measures from which can be selected those applicable to each patient. Rest for the patient as well as for his joints heads the list. In many cases this means rest in bed. Removal of causes of worry and apprehension in so far as this can be accomplished in these times of unrest is as essential as physical repose. Elimination of infection is of first importance in many, and will contribute to the improvement of still other patients.

A well-balanced diet, including milk, eggs, meat, fruit and vegetables, affording full caloric requirement, with ample protein and fat, is important especially in atrophic arthritis. In the obese, reduction of weight will give relative relief from trauma to weight bearing joints. Reduction of carbohydrates may at times decrease local swelling and distress of joints. A diet excessively high in sugar and starches, frequently adopted by patients invalided with arthritis, is undesirable also because it is likely to be deficient in proteins, fat, and vitamins and contains insufficient residue to provide for efficient elimination. An abundant fluid intake will promote elimination by the kidneys and bowel.

Most of the drugs specially devised for the treatment of arthritis have not justified the claims made for them. In general the trend is away from excessive drug therapy in arthritis. Preparations of the salicylic group are useful for their analgesic action. Iron and other antianemic drugs in combination with diet are of great value in combating anemia. Thyroid deficiency, frequently present in chronic arthritis, is met with appropriate doses of thyroid extract. Vaccines as a routine treatment are as ineffective as are certain of the widely heralded drugs. There are, no doubt, many instances in which vaccines have been helpful, but more often they have been used as a sort of occupational therapy by patient and physician, sometimes to the exclusion of more effective agencies.

In addition to measures taken to remedy general anemia and malnutrition of the patient, local treatment to improve nutrition and circulation in the joints is required. Heat, dry and with moist packs, combined with gentle massage increases local blood supply. The degree of active and passive motion to be employed is to be determined in each case, with the necessity of gentleness always in mind. For these purposes, simple appliances and those improvised in the home are desirable. In the past year we have been

treating the cold clammy extremities of atrophic arthritis with negative pressure by means of the Pavaex machine. The skin temperature is increased, and in the small group of selected patients so treated the joints have improved.

Chronic arthritis, especially in its advanced stages, requires skilled orthopedic care. Much may be accomplished in correction of deformities and improvement of posture of the arthritic. More important still is treatment earlier in the disease, to prevent deformities and contractures. If ankylosis is unavoidable, positions of joints most serviceable to the patient should be secured.

In spite of the present popularity of vitamins, it would seem that much of the reputed necessity for vitamins may be obviated by moderate attention to the maintenance of a balanced diet including the conventional articles of milk, fresh fruits and vegetables, eggs and meat. In so far as there is probability of an unavoidably incomplete diet or lack of sunlight, the vitamin deficiency may be supplied in form and amount necessary for the general welfare of the body. There is still some doubt as to the wisdom of supplying this or that vitamin in large doses for the cure of disease of the joints. Neither is an immediate favorable effect on the joints clearly proved, nor have the more remote, and possible unfavorable effects of massive doses of vitamin-containing substances on human tissues been determined.

Gout is not so rare as some have thought, and may occur alone or in combination with either of the two great types of chronic arthritis. Preparations of colchicum, and appropriate modification of diet are as effective as ever in gout.

Osteochondritis or epiphysitis of the spine originating in rapidly growing children with characteristic lesions involving the vertebral bodies may cause early pain, disability and bone deformity, and in later life contribute to osteoarthritis. The recognition of these lesions by means of the history and by the roentgen-ray will obviate a fruitless search for local infections and suggest necessary rest and support for the painful backs of these youngsters.

Much can be done for the patient with chronic arthritis. Recognition and treatment of his general defects in nutrition and in resistance to infection, and his individual tissue response to injury, are as important as treatment of his joints. The resultant of causes and tissue responses is recorded in the changes already evident in the joints.

Classification of chronic arthritis into atrophic and hypertrophic types is advantageous and practical. While it may express to a varying extent etiologic factors, it is more important as an indication of the aggregate result of both general and local causes which have been active in each patient, and of the probable subsequent course of the disease.

The patient with arthritis is best treated not as one of a crowd, but individually, with reference to his own special problem of general as well as local disease.

TREATMENT OF PNEUMONIA WITH SERUM CONTAINING TYPE-SPECIFIC, HETEROPHILE, AND NEUTRALIZING ANTIBODIES ¹

By VLERNER B CALLOMON, M D , and JOHN UNGAR, JR , M D ,
Pittsburgh, Pennsylvania

THE value of the conventional antipneumococcus sera, both unconcentrated and concentrated, has been shown to lie for the greater part in their content of type-specific protective antibodies. Unfortunately, their field of usefulness has been restricted chiefly to Type I infections, although there is some evidence of activity in Type II and in Types VII and VIII infections ¹. In Type III and most Group IV infections evidence of any curative value is lacking. For some years immunologic observations have been accumulating which have led to the preparation of an antipneumococcus serum containing additional immune factors.

In 1911 Forssman ² observed that the injection of guinea pig tissues into the rabbit results in the production of antibodies which not only react with their homologous antigen, but also hemolyze sheep's red blood cells. Because these antibodies react with antigens other than those which produce them, the term heterophile has been applied to both antibody and antigen. It later developed that this type of antigen is present in a variety of animal and bacterial species, while absent in others. Injection of heterophile antigen into animals in whose tissues it is lacking results in the formation of heterophile antibodies. This does not occur when animals whose tissues contain heterophile antigen are so injected. Among the animal species containing heterophile antigen are the guinea pig, cat, dog, mouse, chicken, and horse. Among those containing none are the ox, rat, rabbit, and man.

In 1931 Bailey and Shorb ³ published the results of experiments from which they concluded that heterophile antigen is present in pneumococci, and in common with heterophile antigen from other sources is capable of inducing the production of heterophile antibodies when injected into the rabbit. These antibodies react with heterologous as well as homologous types of pneumococci. They also reported that serum from human convalescent pneumonia patients shows a definite increase in heterophile antibody titer.

This latter observation has failed of confirmation by Finland, Ruegger, and Felton, who recently reported their inability to demonstrate significant increases in heterophile antibody content of serum from human pneumonia cases or from cases immunized against pneumococcal antigen ⁴.

Further experiments by Bailey and Shorb ⁵ were reported in 1933.

* Received for publication December 13, 1935.

From the Section on Respiratory Diseases, Division of Medicine, Allegheny General Hospital.

These bore out then earlier conclusion that pneumococcus heterophile antibodies are not type-specific, and in addition disclosed that the heterophile antibodies in antipneumococcus rabbit serum are partially neutralized by normal horse serum, and to a greater degree by antipneumococcus horse serum. This, of course, demonstrates the presence of natural heterophile antigen in normal horse serum and the increase of heterophile antigen in antipneumococcus horse serum. Furthermore, they found that the addition of various proportions of antipneumococcus rabbit serum to antipneumococcus horse serum enhanced its opsonic power for pneumococci. This opsonic activity seemed to be intimately associated with the heterophile antibody fraction.

In 1930 Jamieson and Powell⁶ found that some pneumococcus filtrates contain toxic substances which can be demonstrated and measured by intradermal tests in human beings and certain breeds of rabbits. They were able by subcutaneous injection of horses to produce sera having the property of neutralizing these toxic substances. These sera were not type-specific, but appeared active against filtrates of all types of pneumococci. They also observed that serum from convalescent human pneumonia cases contained such skin test neutralizing substances.

In 1933 Powell, Jamieson, Bailey, and Hyde,⁷ realizing that the conventional antipneumococcus horse serum falls short of the ideal because of its content of heterophile antigen and lack of heterophile antibody, carried out experiments with various combinations of antipneumococcus rabbit and antipneumococcus horse serum in the treatment of pneumococcus infections in rabbits. They found that such combinations were much more effective therapeutic agents than either serum used singly.

Laboratory investigation and animal experimentation having given such encouraging leads, a clinical trial of the use of such a preparation in the pneumococcus pneumonias of man seemed indicated. A composite serum has recently been prepared for this purpose. In its preparation horses are immunized by intravenous injections of virulent cultures of Types I, II, III, and IV (Type IV of Group IV of Georgia Cooper) pneumococci, and subcutaneous injections of whole culture toxic vaccine of the same types. When by trial bleedings sufficient type-specific protective potency for Types I and II pneumococci and sufficient neutralizing value has been determined, the serum is drawn, refined, and concentrated. Rabbits are immunized by intravenous injection of the same types of pneumococci. Their serum is tested for heterophile antibody, refined, and concentrated. The horse and rabbit antisera are then mixed in such proportions that the heterophile antigen present in the horse serum is precipitated and filtered out, and a final titer reached of 10,000 conventional mouse protective units each of Types I and II, 100,000 skin test neutralizing units,⁶ and 50,000 heterophile antibody units⁷ in each therapeutic dose.* In comparing the finished product with

* Description of preparation taken from information received from Eli Lilly and Company, Indianapolis, Ind., whose generosity in supplying the serum used in this study is gratefully acknowledged.

the hitherto available conventional, concentrated sera of the Felton type, it is at once apparent that they are alike in their content of type-specific protective antibodies against Types I and II, but differ in that in the composite serum heterophile antigen has been eliminated and heterophile and neutralizing antibodies have been added

Experience with the use of this serum in the treatment of a series of cases of pneumococcus pneumonia in Pittsburgh during the season of 1934 to 1935 forms the basis of this report. It was planned arbitrarily to select for this treatment cases of proved pneumococcus pneumonia which came under observation not later than the fourth day of their disease, and which were not obviously complicated. As will appear, a few cases received serum therapy which were later found not to have these qualifications. These latter cases will receive separate consideration. Before instituting serum treatment, in addition to a history, physical examination, blood count, and sputum examination, a roentgen-ray of the chest was taken when possible in order to establish the diagnosis conclusively. Blood cultures were taken at two-day intervals in all cases but one which was treated outside of the hospital. Sputum was regularly typed, but no attempt was made to further differentiate members of Group IV. Following the establishment of the diagnosis, a therapeutic dose of serum was given intravenously at four- to six-hour intervals for approximately 10 doses, or until the fever subsided and showed no tendency to rise again. Prior to giving the serum, intracutaneous and ophthalmic tests were made to avoid dangerous serum reactions. Supplementary treatment consisted only of limitation of diet to liquids including an adequate supply of fruit juice fortified with dextrose, daily enemas as required, and symptomatic medication, such as oxygen and morphine, when indicated. Of 32 cases treated by this method, 24 cases are included in this series as having all the qualifications originally demanded. Brief case outlines follow.

CASE REPORTS

Case 1 J L W, male, Indian, aged 42. Admitted November 19, 1934. Lobar pneumonia, right upper lobe. Onset one day prior to admission. Sputum pneumococcus Group IV. Blood culture negative. Roentgen-ray confirmatory. Serum treatment instituted on third day of disease 24 hours after admission. Five ampoules of serum given in 40 hours. Death occurred on fifth day of disease. Autopsy lobar pneumonia with multiple abscesses of lung.

Case 2 J F, male, white, aged 49. Admitted November 26, 1934. Lobar pneumonia, right hilus. Typical onset one day prior to admission. Sputum pneumococcus Type I. Blood culture pneumococcus Type I. Roentgen-ray confirmatory. Five ampoules serum given within 24 hours after admission. Recovery by rapid lysis.

Case 3 N S, male, white, aged 68. Typical onset, December 8, 1934. Lobar pneumonia, right lower lobe. Sputum pneumococcus Group IV in large numbers. Blood culture not taken. W B C, 24,200. Serum started 17 hours after onset. Three ampoules at six hour intervals. Recovery by crisis.

Case 4 J H, male, white, aged 44. Admitted January 5, 1935. Lobar pneumonia, whole right lung. Onset one day prior to admission. Sputum pneumococcus

Type I Blood culture pneumococcus Type I W B C, 30,650 Roentgen-ray confirmatory Eight ampoules of serum given within 48 hours after admission without terminating illness Type I convalescent whole blood (250 c c) given over fifth, sixth, and seventh days of illness Recovery on seventh day of illness

Case 5 T E, male, white, aged 57 Admitted February 7, 1935 Lobar pneumonia Onset two days prior to admission with pain but no chill Sputum pneumococcus Type II Blood culture negative W B C, 28,900 Roentgen-ray confirmatory Four ampoules serum given within 24 hours after admission Recovery by rapid lysis

Case 6 D K, male, white, aged 40 Admitted February 12, 1935 Postoperative lobar pneumonia, right lower lobe Onset one day following herniorrhaphy Sputum pneumococcus Group IV in large numbers Blood culture negative W B C, 17,600 Roentgen-ray confirmatory Serum started first day Six ampoules serum given Recovery by rapid lysis

Case 7 N K, male, white, aged 55 Admitted February 18, 1935 Lobar pneumonia, right lower lobe Typical onset one day prior to admission Sputum pneumococcus Type III Blood culture negative W B C, 13,000 Roentgen-ray confirmatory Four ampoules serum given within 24 hours after admission Recovery by rapid lysis

Case 8 J M, male, white, aged 72 Admitted March 21, 1935 Lobar pneumonia, left upper lobe Post-tuberculous fibrosis of both apices Onset of pneumonia four hours prior to admission Sputum pneumococcus Group IV and some streptococci Blood culture negative W B C, 28,350 Roentgen-ray confirmatory One ampoule serum given five hours after onset Recovery by rapid lysis

Case 9 M B, male, black, aged 25 Admitted March 29, 1935 Lobar pneumonia, left lower lobe Typical onset seven hours prior to admission Sputum pneumococcus Group IV Blood culture negative W B C, 17,000 Roentgen-ray confirmatory Eight ampoules of serum given in 48 hours Recovery by rapid lysis

Case 10 G B, male, white, aged 42 Admitted April 5, 1935 Lobar pneumonia, left lower lobe Typical onset five hours prior to admission Sputum pneumococcus Group IV Blood culture negative W B C, 22,000 Roentgen-ray confirmatory Eight ampoules of serum given Recovery by rapid lysis (Figure 1)

Case 11 G P, male, white, aged 35 Admitted April 15, 1935 Lobar pneumonia, right upper and middle lobes Nephritis Chronic alcoholism with delirium tremens Onset two days prior to admission, three days before serum Sputum pneumococcus Type I, few Vincent's organisms Blood culture negative W B C, 23,350 Roentgen-ray confirmatory Urine heavy albumin and many casts Blood chemistry N P N 66 mg, Urea N 54 mg Eight ampoules serum in 28 hours Rapid fall to normal in 24 hours Temperature rose following day with development of marked delirium Three more ampoules serum given Developed marked bradypnea, cyanosis and some nuchal rigidity Spinal fluid increased pressure, but otherwise normal Death on sixth day

Case 12 Mrs C F, female, white, aged 35 First seen April 19, 1935 Lobar pneumonia, whole left lung Empyema Typical onset 28 hours before seen Sputum pneumococcus Group IV in great numbers Blood culture negative W B C, 28,000 Roentgen-ray not taken (patient at home) Ten ampoules of serum given in 48 hours Defervescence by gradual lysis to normal, followed by secondary moderate rise due to empyema Pus from pleura pneumococcus Type II Thoracotomy with rib resection Recovery

Case 13 J B, male, white, aged 31 Admitted April 20, 1935 Lobar pneumonia, left lower lobe Typical onset two days prior to admission Sputum pneumococcus Type III Blood culture negative W B C, 14,550 Roentgen-ray con-

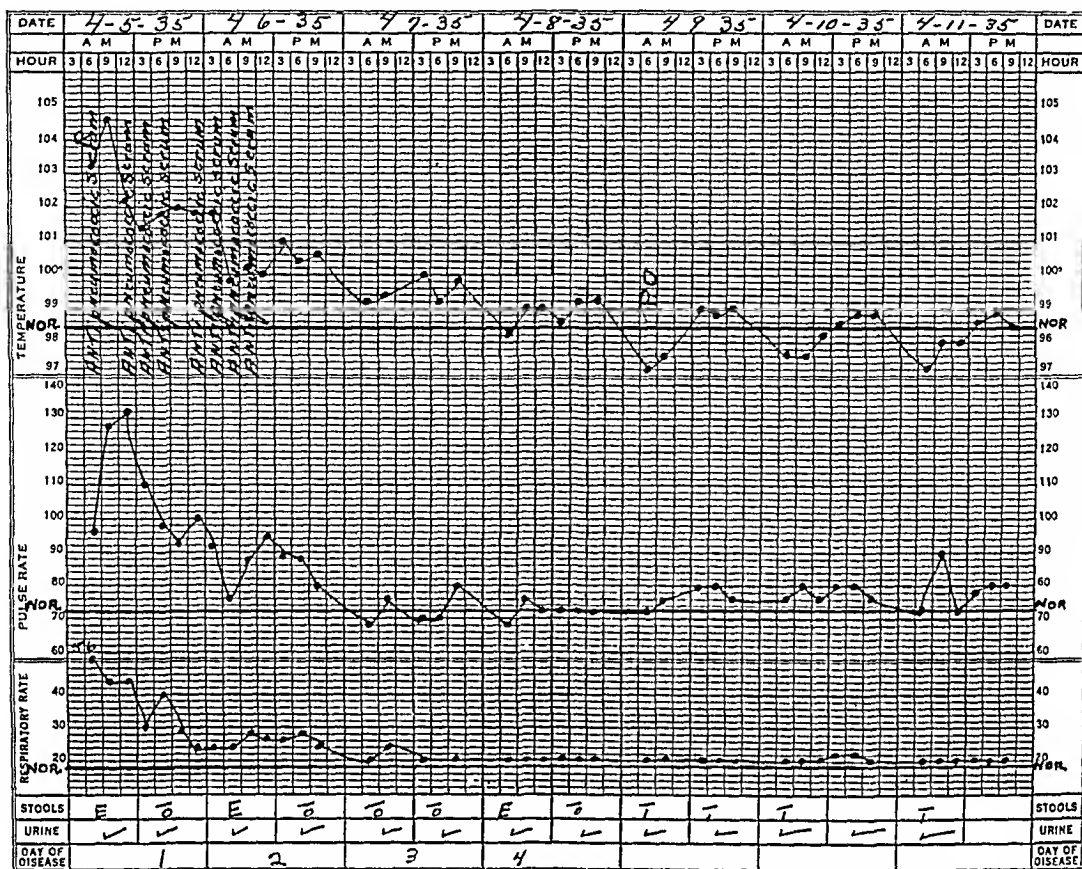


FIG 1 Case 10, G B Lobar pneumonia, left lower lobe Pneumococcus Group IV

firmatory Four ampoules serum given in 24 hours Recovery by crisis in 24 hours (Figure 2)

Case 14 G S, male, white, aged 64 Admitted April 22, 1935 Postoperative lobar pneumonia, whole left lung Onset one day following herniorrhaphy Sputum pneumococcus Group IV Blood culture negative W B C, 17,300 Roentgen-ray confirmatory Nine ampoules serum started 30 hours after onset and given within 30 hours Recovery by rapid lysis within 30 hours

Case 15* J M, male, white, aged 58 Admitted April 27, 1935 Lobar pneumonia, left lower lobe Typical onset 10 hours prior to admission Sputum pneumococcus Group IV Blood culture negative W B C, 14,450 Roentgen-ray confirmatory Eight ampoules serum given within 48 hours Recovery by lysis on fourth day

Case 16† W H J, male, white, aged 40 Admitted April 28, 1935 Lobar pneumonia, right lower lobe Typical onset two days prior to administration of serum Sputum pneumococcus Type III Blood culture negative W B C, 18,000 Three ampoules of serum given in 12 hours Recovery by rapid lysis

Case 17 C G, male, white, aged 68 Admitted May 2, 1935 Lobar pneumonia, whole right lung Chronic and acute alcoholism Typical onset one day prior to admission Sputum pneumococcus Type III and many Vincent's organisms Blood culture pneumococcus Type III W B C, 10,300 Roentgen-ray con-

* Reported by kind permission of Dr C Wm G Schaefer

† Reported by kind permission of Dr John A O'Donnell

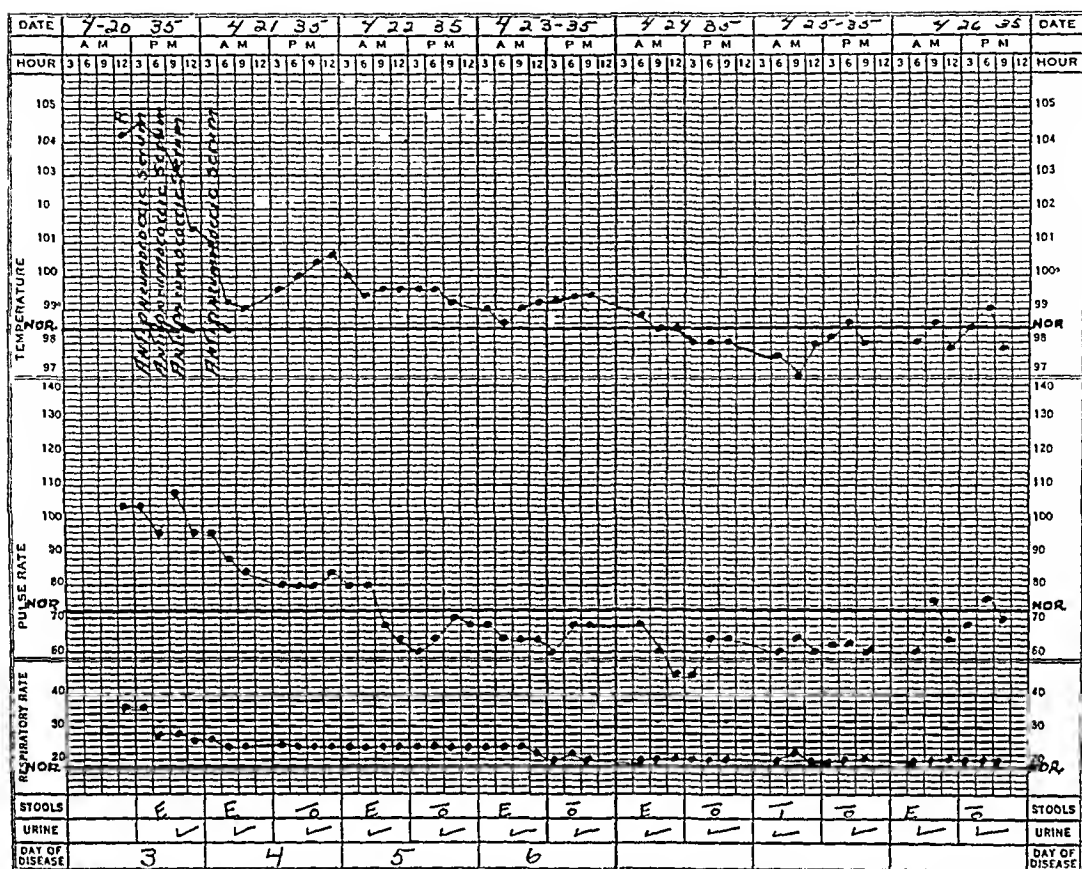


FIG 2 Case 13, J B Lobar pneumonia, left lower lobe Pneumococcus Type III

firmatory Eight ampoules of serum given in 48 hours Death on eighth day Autopsy Lobar pneumonia Right empyema, not diagnosed during life

Case 18 F M, female, white, aged 18 Admitted May 6, 1935 Lobar pneumonia, left lower lobe Typical onset 36 hours prior to admission Sputum pneumococcus Group IV Blood culture negative W B C, 26,500 Roentgen-ray confirmatory Seven ampoules serum given within 48 hours Recovery by rapid lysis on fourth day of illness

Case 19* S A W, male, white, aged 53 Admitted May 6, 1935 Lobar pneumonia, whole left lung, empyema Onset three days prior to administration of serum Sputum pneumococcus Group IV Blood culture pneumococcus Group IV, showing 50, 50, 15, and 0 colonies per c c W B C, 29,750 Roentgen-ray confirmatory Eleven ampoules serum given over four days, interval of 40 hours between second and third ampoules of serum Recovery by gradual lysis, with secondary rise due to empyema Thoracotomy with rib resection Recovery

Case 20 G Z, male, white, aged 21 Admitted April 30, 1935 Lobar pneumonia, whole right lung Onset one day before admission with pain and bloody sputum but no chill Sputum pneumococcus Group IV and many streptococci Blood culture negative W B C, 21,900 Roentgen-ray confirmatory Ten ampoules of serum given in 48 hours Recovery by crisis on fifth day

Case 21 N R, female, white, aged 16 Admitted May 13, 1935 Postoperative lobar pneumonia, left hilus Onset one day following appendectomy Sputum pneu-

* Reported by kind permission of Dr J R Simon

mococcus Group IV Blood culture negative W B C, 25,000 Roentgen-ray pneumonia, left hilus Four ampoules serum given within 24 hours Recovery by rapid lysis

Case 22 L S, male, white, aged 54 Admitted May 27, 1935 Postoperative lobar pneumonia, right upper lobe Onset with chill one day following prostatic resection Sputum pneumococcus Type III Blood culture negative W B C, 25,150 Roentgen-ray confirmatory Ten ampoules of serum given in 48 hours Recovery by lysis

Case 23 R S, Male, white, aged 72 Admitted May 28, 1935 Lobar pneumonia, right lower lobe Typical onset two days prior to admission Sputum pneumococcus Type II Blood culture negative W B C, 28,750 Roentgen-ray confirmatory Nine ampoules of serum given in 36 hours Recovery by rapid lysis

Case 24 J M, male, black, aged 53 Admitted June 5, 1935 Lobar pneumonia, whole left lung Onset three days prior to admission with fever, cough, pain, and bloody sputum, but no chill Sputum pneumococcus Type III, streptococci, Vincent's organisms, Leptotrix Blood culture negative W B C, 45,300 Roentgen-ray confirmatory Ten ampoules of serum given in 48 hours Recovery by lysis After one week of practically normal temperature and well being, moderate fever again developed and roentgen-ray showed left lower lobe entirely cleared, but very dense shadow in left upper lobe and considerable infiltration of peribronchial variety in right upper lobe Abscess, tuberculosis, or neoplasm suspected Patient, upon his own insistence, left hospital before accurate diagnosis could be established

Brief outlines follow of those cases which, after serum treatment was instituted, proved to be lacking in certain of the qualifications demanded for admission to the above series

Case A D T, male, black, aged 24 Admitted November 26, 1934, with diagnosis of lobar pneumonia, right upper lobe Onset about one week prior to admission with fever and pain, but no chill Variable signs over right upper lobe Sputum pneumococcus Group IV and Vincent's organisms Blood culture negative W B C, 10,000, 10,500, 10,100 Roentgen-ray shadow over right upper lobe Wassermann 3 plus Six ampoules serum given in first 48 hours with no effect After 12 days in hospital, course of neoarsphenamine given and patient recovered by slow lysis The finding of many Vincent's organisms in the sputum with negative blood culture, comparatively low leukocyte count, lack of any noticeable effect on the course from serum administration in contrast to gradual defervescence over a period of three weeks under neoarsphenamine administration, might well justify a diagnosis of pulmonary spirochetosis rather than pneumococcus pneumonia

Case B C D, female, white, aged 22 Admitted February 6, 1935 Postoperative lobar pneumonia, left lower lobe Onset probably one day following biopsy and cauterization of cervix Sputum not sent until one week after recovery, when it showed streptococcus Blood culture negative W B C, 12,500 on fifth day postoperative Roentgen-ray confirmatory Serum started on fourth day postoperative Three ampoules serum given Recovery on sixth day postoperative Although physical signs and roentgen-ray evidence of pneumonia were present and response to serum administration was typical, there is no proof that this pneumonia was due to pneumococcus infection

Case C H M, male, white, aged 17 Admitted March 6, 1935 Lobar pneumonia, left lower lobe Marked malnutrition Delirious on admission Onset two days prior to admission Sputum bedside direct smear, pneumococcus (?) Blood culture negative W B C, 23,100 Roentgen-ray confirmatory Urine heavy albumin and much pus Six ampoules of serum given Death in 45 hours While pneumococci were thought to be present in the sputum at bedside examination, no

laboratory confirmation of this finding is available. Moreover, inasmuch as the urine was reported to contain a heavy cloud of albumin and a large quantity of pus, it is quite possible that this patient may have been suffering from generalized infection secondary to disease in the genito-urinary tract.

Case D J S, male, white, aged 18. Admitted March 9, 1935. Lobar pneumonia, right upper and lower lobes. Right empyema. Bronchopneumonia and fibrinous pleurisy in left lung. Onset five days prior to admission. Sputum pneumococcus Group IV. Blood culture negative. Culture from empyema hemolytic streptococcus W B C, 22,000. Roentgen-ray confirmatory. Nine ampoules serum given within 48 hours after admission with no apparent effect. Recovery by lysis after surgical drainage. Even though Group IV pneumococci were recovered from the sputum, there was evidence of fluid in the right chest on admission, hemolytic streptococci rather than pneumococci were recovered from the pleural exudate, and defervescence gradually occurred after drainage of the empyema. The streptococcus infection was probably dominant.

Case E H G, male, white, aged 22. Admitted March 9, 1935. Lobar pneumonia. Loculated empyema and fibrinous pericarditis. (These present on admission.) Onset with chill four days prior to admission. (This information questionable.) Sputum pneumococcus Group IV. Blood culture pneumococcus Type II. Pleural fluid pneumococcus Type II W B C, 20,000. Roentgen-ray confirmatory. Seven ampoules serum given. Several aspirations of chest. Death 48 hours after admission. Autopsy confirmed clinical findings. Due to the fact that the empyema was loculated, adequate drainage could not be obtained.

Case F H R, male, white, aged 31. Admitted May 9, 1935. Lobar pneumonia, whole right lung. Typical onset two days prior to admission. Sputum pneumococcus Group IV, tubercle bacilli, Vincent's organisms. Blood culture pneumococcus Group IV W B C, 18,150. Roentgen-ray confirmatory. Twelve ampoules serum in 48 hours. Recovery from pneumonia by slow lysis. Sent to tuberculosis sanatorium.

Case G W R, male, black, aged 48. Admitted May 16, 1935. Lobar pneumonia, whole left lung, right upper and middle lobes. Active pulmonary tuberculosis. Diabetes mellitus. Typical onset one day prior to admission. Sputum pneumococcus Group IV and many tubercle bacilli. Blood culture negative W B C, 15,950. Roentgen-ray confirmatory. Urine sugar 4 plus. Blood sugar 308 mg. Nine ampoules of serum given in 48 hours. Temperature fell by crisis on seventh day, however, a secondary rise associated with symptoms of meningeal irritation occurred two days later, and death occurred on eleventh day. Spinal fluid globulin 1 plus, 60 cells, mostly lymphocytes. Autopsy lobar pneumonia as above, pulmonary tuberculosis.

Case H A C, male, black, aged 60 (?). Admitted July 8, 1935. Lobar pneumonia, whole right lung. Onset three days prior to admission. Sputum pneumococcus Type III. Blood culture pneumococcus Type III W B C, 50,000. Urine sugar 4 plus, acetone and diacetic acid positive. Blood chemistry N P N 61.6 mg, sugar 652 mg. Roentgen-ray confirmatory. Three ampoules serum given in 15 hours, temperature, pulse, and respiration dropped rapidly to normal. However patient became stuporous and comatose and temperature again rose and patient died of diabetic coma 24 hours after admission. Reports of blood chemistry and urine not received in time to institute treatment.

COMMENT

In the following discussion only the 24 cases of proved pneumococcus pneumonia admitted not later than the fourth day of their disease and not obviously complicated are considered.

One of the outstanding impressions received in observing this group of cases was the relative absence of symptoms and signs of severe toxicity. Although quite aware of the impossibility of accurately measuring manifestations of toxicity, we were struck by the low incidence of marked cyanosis, by the relatively low degree of respiratory embarrassment, the improved quality of the pulse, and the low incidence of delirium and tympanites after serum had been administered.

In evaluating specific therapy for an acute febrile illness of known duration, one of the most important factors is its ability to shorten the course of the disease as well as alter its severity. From a review of the above case abstracts this property of the serum is strongly suggested. It may be rightfully objected that an occasional case of pneumonia may terminate in less than the classical seven days, yet one could hardly anticipate this in as high a percentage of cases as occurred in this series. Of the 24 fully qualified cases which were serum treated, 16 (numbers 2, 3, 5, 6, 7, 8, 9, 10, 13, 14, 15, 16, 18, 20, 21, and 23) recovered by rapid lysis or crisis.

No mortality statistics on the basis of so limited a series warrant any definite conclusions. Experience with the treatment of this disease shows that its mortality varies from season to season and even from month to month. It may be remarked, however, that the death rate from pneumonia in Pittsburgh is always comparatively high, in fact it is usually not exceeded by that in any other of the large cities of the United States. It is equally impossible to maintain adequate control in estimating the value of a curative agent because the number of variables, such as age, virulence of infection, degree of blood invasion, previous state of nutrition and health, stage of disease upon admission, etc., is legion. Nevertheless a comparison of the mortality rate in this series and that in a group of approximately the same number which were treated in this hospital at about the same time without serum is interesting and, we believe, suggestive. The control series was comprised of those proved cases of pneumococcus pneumonia without obvious complications which either entered the hospital in the few weeks before the trial of serum treatment was initiated or during the periods when our supply of serum was exhausted, those which were admitted later than the fourth day of the disease, and those which were private patients of other physicians in the hospital and not under our control. Most of these cases received small doses of quinine in addition to the hygienic and symptomatic treatment outlined above. Of 24 serum-treated cases three died, a mortality of 12.5 per cent. Of 26 cases* treated without serum 10 died, a

* Of these, one case which recovered, and one which terminated fatally were not typed. Excluded from the control series were one case complicated by pyelonephritis and phlebitis, one case by diabetes mellitus, one case by parturition, four cases by asthma, one case by pulmonary fusospirochetosis and lung abscess, one case by rheumatic arthritis, and one case by chronic heart disease with decompensation.

Thus far in the 1935 to 1936 pneumonia season ten additional cases have been serum treated, with nine recoveries (including three with positive blood culture) and one death. These will receive further analysis in a subsequent report covering the current season's experience.

Grateful acknowledgment is made to Miss Edith Culbert for valuable aid in the preparation of accurate records.

mortality of 38.5 per cent. It is true that the average age in the serum-treated group was 47 while that in the control group was 50. However, of five cases aged 60 or more in the serum-treated group one died, a mortality of 20 per cent, while of 10 cases above 60 years of age in the control group six died, a mortality of 60 per cent.

Analyzing the mortality as to type, we find that of three cases of Type I infection treated with serum, one case died, of two cases of Type I infection in the control series, both recovered. There were no deaths among three serum-treated cases of Type II infection, while one case out of three in the control group died. Of particular interest is the comparison in the Type III and Group IV cases, against which the serum contains no type-specific protective antibodies. Of six cases of Type III infection in the serum-treated group, one died, a mortality of 16.7 per cent, while three cases out of eight in the control group died, a mortality of 37.5 per cent. One case out of 12 in the serum-treated series of Group IV infections died, a mortality of 8.3 per cent, while of 11 in the control series five died, a mortality of 45.4 per cent. This marked discrepancy in mortality in the latter two groups gives support to the thesis that heterophile antibody and skin test toxin neutralizing bodies are of considerable value in the control of these infections.

Of four serum-treated cases with positive blood cultures one died. Of nine cases with positive blood cultures in the control series four died. Parenthetically, it is interesting to note that of three fatal cases in the serum-treated series, only one had a positive blood culture, and of 10 fatal cases in the control series only four had positive blood cultures. As opposed to the 25 per cent mortality in the four cases with positive blood cultures in the serum-treated series, there were two deaths among 20 cases or a mortality of 10 per cent in the cases with negative blood cultures. Whereas, in contrast to the 44.4 per cent mortality among the nine cases with positive blood cultures in the control series, there were six deaths among 17 cases with negative blood cultures, a mortality of 35.3 per cent.

If all cases to which serum was administered, regardless of their qualifications, were taken into consideration, the series would consist of 32 cases with seven deaths, a mortality of 21.8 per cent. The Type I mortality would be unaffected. There would be four cases of Type II infection with one death. There would be two deaths among seven cases of Type III infection, a mortality of 28.5 per cent, and two deaths among 16 cases of Group IV infection, a mortality of 12.5 per cent.

If all cases treated without serum, regardless of complications, were included in the control series, the latter would consist of 36 cases with 17 deaths, a mortality of 47.2 per cent. The Type I mortality would be unaffected. There would be five cases of Type II infection with three deaths. There would be four deaths among nine cases of Type III infection, a mortality of 44.4 per cent, and eight deaths among 17 cases of Group IV infection, a mortality of 47 per cent.

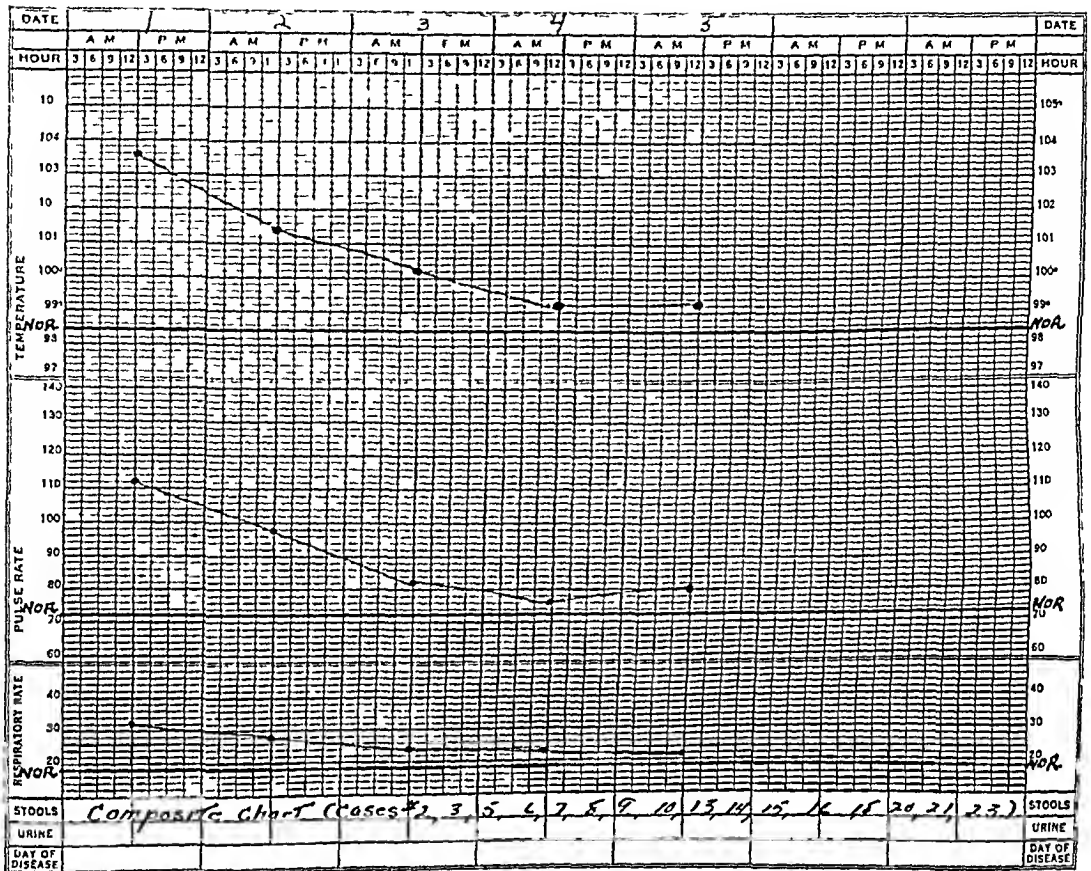


FIG 3 Composite chart Cases 2, 3, 5, 6, 7, 8, 9, 10, 13, 14, 15, 16, 18, 20, 21, and 23

It should be noted that, judging from the experience with this series of cases (cases number 12, 17, 19, and E), this serum given intravenously seems to have no anti-bacterial activity against pneumococci that have gained access to the pleural sac

In the early days of the study serum was given at six-hour intervals. Later the interval was reduced to four hours with, we believe, better results. The number of ampoules given varied from one to twelve, the majority of cases receiving eight ampoules. Chill reactions were frequent in the early cases following administration of the first allotment of serum received, none of which, however, proved serious. Since that supply was exhausted such reactions have been remarkably rare. Serum sickness of the usual type, characterized by urticaria, joint pains, and low-grade fever occurred approximately one week after administration in 14, or 56 per cent, of the 25 cases which recovered.

As the most striking effect of the administration of this serum thus far observed appeared to be a prompt, premature defervescence, a composite chart (figure 3) was prepared by plotting the average daily temperature, pulse, and respiratory rate in 16 cases (cases number 2, 3, 5, 6, 7, 8, 9, 10,

13, 14, 15, 16, 18, 20, 21 and 23) responding by crisis or rapid lysis. The curve begins with the records immediately preceding the first dose of serum.*

The question of whether the outcome of the disease is influenced by the stage at which treatment is instituted cannot be answered from this study, since serum treatment was limited to cases admitted not later than the fourth day of their disease. Further investigation is necessary to determine whether this type of serum treatment has value in cases seen late in the course of their infection. The question of optimal dosage also requires further study.

SUMMARY

Experimental observations of various investigators have been cited which indicate that the efficacy of the conventional type-specific antipneumococcus horse serum is enhanced by the addition of heterophile antibody and antibodies which have the property of neutralizing toxic substances in pneumococcus filtrates.

Experience with the use of such a modified antipneumococcus serum in the treatment of a series of 32 cases of pneumococcus pneumonia in Pittsburgh during the 1934 to 1935 season has been outlined and the results analyzed. Comparison has been drawn between the results in this series and those in a similar series treated without benefit of serum administration. While the series is relatively small and dogmatic conclusions therefrom as to effect on mortality are probably not warranted, certain deductions may, we feel, be reasonably drawn.

CONCLUSIONS

- 1 Serum-treated cases appear definitely less toxic than those not so treated.

- 2 The febrile course of a large percentage of cases of pneumococcus pneumonia of all types treated with serum was prematurely terminated.

- 3 The efficacy of the serum in Type III and Group IV cases is particularly striking as these infections have not been favorably influenced by the administration of the available conventional antipneumococcus sera.

- 4 Antipneumococcus horse serum modified by the addition of heterophile antibody and neutralizing antibodies for toxic substances in pneumococcus filtrates constitutes a promising new agent in the therapy of pneumococcus pneumonia.

BIBLIOGRAPHY

- 1 Statistical reports to date summarized by BELK, W. P. The specific treatment of lobar pneumonia, Jr. Am. Med. Assoc., 1935, cv, 868.
- 2 FORSSMAN, J. Die Herstellung hochwertiger spezifischer Schafhamolysine ohne Verwendung von Schafblut. Ein Beitrag zur Lehre von heterologer Antikörperbildung, Biochem. Ztschr., 1911, cxvii, 78.

* *Editor's note.* Charts of the temperature, pulse and respiration of the majority of the serum-treated cases were furnished by the author but lack of space forbade their publication.

- 3 BAIFFY, G H, and SHORR, M S Heterophile antigen in pneumococci, *Am Jr Hyg*, 1931, *xiii*, 831
- 4 FINLAND, M, RUGSEGGER, J M, and FELTON, L D Heterophile antibodies in pneumonia, *Jr Clin Invest*, 1935, *xiv*, 683
- 5 BAIFFY, G H, and SHORR, M S Immunological relationships of pneumococci and other heterophile antigens and biological significance in pneumococcus infections, *Am Jr Hyg*, 1933, *xvii*, 358
- 6 JAMIESON, W A, and POWELL, H M Further studies on the immunology of the pneumococcus, *Am Jr Hyg*, 1931, *xiii*, 823
- 7 POWELL, H M, JAMIESON, W A, BAIFFY, G H, and HINE, R R A comparative study of antipneumococcus serum containing heterophile antibody, *Am Jr Hyg*, 1933, *xvii*, 102

SOME FACTORS IN THE ETIOLOGY OF THE PSYCHONEUROSES *

By LOUIS CASAMAJOR, M D , *New York, N Y*

THE first factor of importance in the understanding of the etiology of the psychoneuroses is that they are not clinical states in the sense of diseases but rather they are states of mind. These patients come to physicians for treatment, and their symptoms are usually referable to one of the bodily systems, but the physician must recognize that they represent not something which has happened inside the patient but something which has happened to the relationship of the patient to the world in which he has to live. Thus each psychoneurosis is an expression of the reactions of the individual toward certain factors of his life which he is unable to handle in a manner compatible with health.

One might well ask what has health to do with the reactions of a patient to his life's problems? It would have nothing to do with it were it not for the fact that sickness may be an asset to the patient. Sickness is incapacitating surely and takes one to the doctor, but often sickness likewise may have an asset value in that it serves as an excuse that permits one to neglect to do things that would be required of one who is well. The Monday morning headache of the child who has not prepared his home work is the prototype of many neurotic symptoms that may appear later in life—when again the needs of existence appear to be too much for one to meet. The asset element in many of the neurotic symptoms of adult life lies in the fact that they absolve one of the responsibility of acting like a normal healthy individual. We pity the sick, excuse them from many things and afford them special treatment, and it is just this special treatment that the neurotic is searching for with his symptomatology.

Within the scope of such a paper it would be impossible to go into the psychology of the psychoneurotic symptomatology. Here one can only draw the line, somewhat arbitrarily, between conscious, deliberate fabrication of symptoms in which the patient himself does not really believe—which is malingering—and the unconscious assumption of symptoms in whose reality the patient stoutly believes—which is neurosis. Charcot expressed this distinction in his famous dictum "The hysteric is a malingerer who does not lie." This succinct sentence expresses all that I have space to say before I go on to etiological factors.

The *raison d'être* then of the psychoneurosis is the fact that it permits the patient to escape from complete responsibility for himself. Responsibility to others and to the world in which we live is in good measure the product of civilization. The more complex our civilization the greater are

* Presented at the Detroit meeting of the American College of Physicians, March 3, 1936.

the responsibilities of each individual member. One may refer it, as Trotter did, to the herd instinct, but whatever it is there can be no doubt that the average man can not live in comfort and happiness unless he has the good opinion of those in whose company he lives his daily life. We sum these factors up in the expression "public opinion," and each man must bask in some degree of that in order to preserve that good self opinion which is so essential to normal life.

The mores of the group may press most heavily upon an individual, but nevertheless he feels he must conform to them if he is to hold his head up among his fellows. There are ideals in public opinion which most of us feel we must at least compromise with even if we are not inclined to conform to them. There are those who feel this way about religious ideals but their number seems to have diminished in recent years. Even where this diminution has occurred not dissimilar ideals of an ethical and a social nature have taken their place with equal force. Ideals of decency and honesty, of fair dealing and "square shooting," of loyalty and honor, of duty and that rather vague thing which is spoken of as "social consciousness" are just as potent as those other similar ideals which are based on worship and reverence. The taboos attached to these social concepts may not be violated unless one is sick, and neurosis is one of the sicknesses that permit it. Not only must the violation not be in reality but it must not be even in the thoughts and wishes of the individual. Of this he is frequently more afraid than he is of any possible infraction in real life. The former is quite as damaging to self respect and, because it has never reached any real expression, it is all the more frightening and hence productive of neurotic symptoms.

Were life as simple as perhaps it should be, were all our motives as nobly inspired as we would like to have the world believe, no one would be beset with the sort of conflicts which form the basis for the psychoneuroses. Man is a social animal, but he is not only that. More fundamental than the social side of human life is the individual, selfish, egocentric side which expresses itself in the doctrine of "every man for himself and the devil take the hindmost" that determines much more of human conduct than do the social, altruistic motives of which we like to boast. This is the sort of conflict that calls for a resolution in every one of us. That resolution may be an adjustment of the personality compatible with health or, when it breaks down, a psychoneurosis. The individual and the social are often opposing forces which pull the erring human in many ways, and one, at least, of these ways leads to neurosis.

Man plays, at best, a dual rôle in many of his activities, and this would be of little consequence were it not for the fact that both ends of this duality are mutually incompatible. The more incompatible the components of this conflict the greater is the possibility of the conflict eventuating in a neurosis. Such a conflict as that between man as a decent member of a civilized society and man as a mammal, or between man as an idealistic social being and man

as a greedy individualist, requires considerable mental adjustment and adaptation to reach a level of solution. This solution may be one compatible with mental health—an adequate one such as most of us succeed in attaining and maintaining most of the time—or an inadequate one in which the need for sickness plays a part of varying importance. Such inadequate solutions may be benign or malignant. The benign reactions are those which permit the individual to lead something approximating a normal life even though a sick one, which is the psychoneurosis, while in the malignant reactions the patient has cast aside all pretense of a normal life to live in a world of his own fantasy, which is psychosis of the schizophrenic sort.

But we must confine ourselves to the psychoneurosis and try to outline some of the factors which stand in conflict with the social man. Primarily these are things of the instincts. One runs the risk of treading on debatable ground when one speaks of instincts. So much has been said and written on this subject that one can find a plenty of opinion either to establish or deny the importance of these primitive motives. This is not the place to indulge in such a controversy. We must assume merely that there are trends in human and other animal life which are not learned and which are common to most of the members of a species. By instincts one need mean little more than this.

It is convenient to divide instincts into two groups: (1) instincts of self preservation, and (2) instincts of preservation of the species. The former may be called the ego instincts and the latter the sexual instincts. In the discussion of the etiology of the neuroses the sexual instincts have played a very prominent role. Perhaps this may have been too prominent, but it is doubtful if this could be the case. It is doubtful if there exists in animal life a force more potent than sex. In defining sex one must not restrict the definition to those physical activities which tend to eventuate in the preservation of the species. The term sexual must cover all of those activities, physical and mental, which appertain to the phenomenon of human mating. Nothing is more interesting to the majority of the human race than this, and nothing occupies human thought to a greater extent. Plato's description of the sexual urge as "an imperious head-strong power" is as accurate today as ever. It is the motive most fitting of all to come in conflict with the ideals of a self-conscious, repressed society. It is true that improper handling of sexual urges in a mind-bound society by inadequate individuals brings to us the majority of our psychoneuroses, but all psychoneuroses are not based upon sex.

The other instinct of self preservation is just as capable of producing psychoneurotic reactions when improperly handled as is the sexual, and it is of this group especially that I wish to speak. The instinct of self preservation is often of even less respectability than is the sexual. It tends to express itself in motives that may have even less of social value than the other. Such egocentric motives as fear and greed are potent forces in all of us but they are never pretty things. Most of us are even more ashamed of them

than we are of our sexual urges. Potent they are in individual life, but on the social plane they are frequently shameful, hence they are ideally fitted to form the basis for that sort of conflict in the personality that leads to neurosis.

Fear is a normal component of animal psychology. It is a direct expression of the instinct of self preservation. Not only is there fear of death which is but an expression of the wish to live, but there are other fears which constantly beset the individual in a civilized society. Fear of injury, fear of exposure and of shame, fear of loss of position and respect, fear of the future, both here and hereafter, and fear of the loss of the feeling of personal security are quite as competent causes of the psychoneurosis as is anything in the sexual life. Life is necessary for man, but even more necessary often, for civilized man, is comfortable life which is not possible without a high opinion of himself and an adequate measure of approval from public opinion.

Greed is another motive all too human. Frequently we like to call it by other more euphonious names especially when we see it in ourselves. It is difficult to appraise it accurately because it is so universal, and even when one sees it in very pure form, such as in some of the litigation and compensation neuroses, one does not like to call it by its real name. Maybe I should not use the word if I feel it calls for so much defense, but I know of no other that expresses so much of what I mean.

If this were all to the ego plane neuroses, just fear and greed, the problem would be simple indeed, but many other motives enter into the make-up. Euphemism and hyperbole play as important a part in the etiology of the psychoneurosis as they do in the symptomatology. Self-respect which is often only another name for conceit, justice which is often indistinguishable from revenge, and the desire for security which may be but a form of indolence may, any or all, enter into the causation of the ego neurosis and cloud the understanding of it with terms that are difficult to define. And when a money value can be placed upon the neurosis as in the compensation neurosis, and legalistic considerations enter into its interpretation, one is faced with a psychological problem of such complexity that simple direct thinking becomes well nigh impossible.

I had hoped in this paper to describe these ego-plane neuroses in which sexual factors play little if any part. They have been described as "situation neuroses" in an attempt to express the idea that situations in the environment of the patient play the more important rôle in the etiology. This is not altogether the case, for while it is true that external considerations hold a prominent place in the causation, yet the personality of the patient and his instinctive ego urges really do the work of formulating the neurosis just as they do the neuroses of sexual origin.

We saw the ego neuroses in their simplest and truest form in the war neuroses—the so-called "shell shock" of the World's War. Back of all of them lay the good old human mechanism of fear—that fear which we all felt

near the front. Some of these cases appeared in camps in this country and others in France at any point up to the front. The clinical picture was the same no matter where they were seen, for the primary cause was the same—fear, which hit different men at different places.

In civil life we have as frequent ego-plane neuroses the compensation-litigation neuroses with which you are all familiar. Usually these follow injury of some sort and hence are known as "traumatic neuroses." The nature and severity of the injury have nothing to do with the make-up of the neuroses. The one point they all have in common is that the injury is compensable. I have yet to see a patient with a traumatic neurosis which resulted from an injury sustained while working for himself.

In business life today ego-plane neuroses not infrequently develop. The present business depression is responsible in a way for some of them, but the ego motives of greed and fear of personal and financial insecurity still form the foundation stones of the etiology. It is interesting to note that the depression has not materially increased the number of our psychoneurotics. This is especially true of those people who are on relief. They have hit the bottom and have nothing left to fear. Life can become nothing but better for them, and on a ground work of such a psychology, psychoneurosis can not find soil to grow. They may become dulled and discouraged or they may become social radicals but the psychoneurosis is not a part of their reactions. It is usually those who still have hopes of surmounting their difficulties and eventually triumphing who hold in their makeup the capacity for psychoneurosis. This is especially true when compensation factors occupy a place in the general life picture. The following cases may illustrate some of the points which I have been trying to make.

CASE REPORTS

Case 1 J. M., aged 58. This man, an uneducated Russian Jew, was brought to this country while still a small child and had been earning his own living since he was eight years of age. As a boy he went into the clothing business and worked his way up until he owned his own factory. He prospered and says he made a great deal of money, and during this time he took out a large amount of life and disability insurance.

In 1927 he began to feel badly but kept on with his work because he had always been a hard worker and knew of nothing else to do. He lost considerable weight and finally "collapsed" at his place of business. When examined by his doctor he was found to have diabetes, under treatment he improved. For the first few months he was able to spend only an hour or so a day at his work, and as a result his business suffered. By 1929 his business was in such bad shape that he decided to close it out, which he did without going into bankruptcy, paying his creditors in full. It is of interest to note that during these years of considerable incapacity he never made any claim upon his insurance company for compensation although he was clearly entitled to it. He felt secure in regard to the future and his ability to earn his living at his trade without relying on compensation. In 1930, after he had closed out his business, he took a position as a salesman with another clothing firm and did well. He continued to work hard, and his employers were sufficiently satisfied with him to renew his contract when it expired. Then something happened to business. He saw it melting away before his eyes. He had always been able to make good adjustments

in a world of good business, but he could find nothing to live by in a world of no business

In June of 1931 he had what he describes as a "breakdown" He began to have headaches, pains all over, dizziness and general weakness These symptoms became gradually worse until he had to give up his work after a few months When I saw him in 1933 his complaints were dizziness, easy fatigability, headache, pains in his arms and legs, insecure gait and station and insomnia The neurological examination was entirely negative He was receiving disability compensation at the rate of \$500 00 a month

It was obvious that this man was suffering from a psychoneurosis and not from any organic disease of the nervous system The question of how much incapacity he had is a difficult one to answer unless one could define "incapacity" He had no means of support except his compensation, and if this were withdrawn he probably could not find enough business to do to support him Support was dependent on his being incapacitated He could not do any work because he thoroughly believed he could not work If his business would pick up he would probably be glad to get into it again and then would not need compensation The fact that he did not ask for compensation when he was organically incapacitated with his diabetes proves that he was not of the sort of personality that malingers His neurosis was caused by the business situation in which he found himself plus the compensation which gave him security and paid him well for staying sick

Case 2 J C, aged 47 This was an agitated, depressed looking man who came in complaining that he could not rest, that he worried all the time and felt a fog in his head In order to understand the condition one had to go back into the history to learn something of the background of this man's development He had been born in Italy, the eldest of 10 children At 16 years of age he came to this country and immediately went to work He always worked hard during the day and attended night school until he was 20 years of age He was interested only in his work and his family and took his responsibilities very seriously He supported his mother and helped his nine younger brothers and sisters to get an education, one of whom graduated from medical school After his marriage he devoted himself to his family, and his only interest was in making money for the support and education of his children

He prospered in the contracting business and built a number of houses, some of which he owned Previous to the stock market crash of 1929 he owned two fifty-family apartment houses and six two-family houses as well as other property Then came the crash of October 1929, which was the beginning of his troubles He was in the market pretty heavily and when stock prices fell he wanted to sell out all his holdings, but his bankers and his brokers insisted that he hold on to them They kept constantly calling on him to put up more money and this he did until he had no more left From being a man of considerable property and a comfortable income he was reduced to absolutely nothing except the \$130 00 a month disability compensation he received from an insurance company Then he became depressed and agitated and constantly walked up and down in his home saying he did not know what he was going to do At times he went around to his bank and complained to the officers that they had not treated him fairly, and they would send for his family to come and get him On one occasion they called in the police to remove him

He continued his worrying, slept badly and talked continuously about what fate had done to him In October 1931 he was placed in a State Mental Hospital where he remained for a year There he lost weight and did not improve mentally When he returned to his home he was calmer but his general mental condition was unchanged

The neurological examination was entirely negative Psychiatrically he appeared depressed and somewhat indifferent and he talked only of the past and of his losses

His stream of mental activity was somewhat underproductive. He did not show any persecutory trend except that he felt he had lost his money as much due to bad advice of bankers and brokers as to anything else, which undoubtedly was not a delusion. His orientation and memory were normal.

This man was suffering from a symptomatic depression of a psychoneurotic sort which is quite understandable when one thinks of what he had been through. It is not difficult to understand the make-up of this depression but it is not quite so easy to see what the outcome will be. As he is at the present time and as business is at the present time he is undoubtedly completely incapacitated. Whether he is permanently incapacitated or not probably depends much more on business conditions than upon himself. Should business pick up and this man be able to borrow some money, build houses and rehabilitate himself there is a good chance that he would recover completely. If prosperity does not return soon it is doubtful if he will ever again be a productive member of society.

If one could consider this man alone and not the social, economic and business situations, one would say that there was nothing in this man to incapacitate him. However, one must appreciate the fact that he is living in the world as it is today, and from that point of view one must say that this man is thoroughly incapacitated at the present time for living in the kind of a world we have in this country today. The compensation he receives is all the security he has at present. If that were taken from him he would most likely go into a deeper depression from which recovery would be most doubtful.

These two cases summarize much better than I can express otherwise the points I have been trying to make in this presentation.

SOLITARY ULCER OF THE ILEUM AND ULCER OF MECKEL'S DIVERTICULUM

By PHILIP W. BROWN, M.D., F.A.C.P., and JOHN DEJ. PENBERTON, M.D.,
Rochester, Minnesota

REPORTS on solitary ulcer of the ileum and on ulcer of Meckel's diverticulum indicate such difficulty in diagnosis, as well as such high surgical mortality that we are endeavoring to present a clearer conception of the problems presented by these two conditions.

There are several excellent reports in the American literature on hemorrhage and perforation attributable to ulcer in or near a Meckel's diverticulum, but little has been written on solitary ulcer of the ileum. In the foreign literature is the paper of Oudard and Jean, who collected reports of 56 cases (37 of ileal ulcer and 19 of jejunal ulcer) in which they noted a 50 per cent mortality among patients whose ulcers were recognized and operated on, while the mortality was 100 per cent if the ulcers had perforated, or if they were not found at operation, or if operation was not undertaken. Aschner and Karelitz reviewed 32 reported cases in which an ileal ulcer was situated at the mouth of a Meckel's diverticulum, with 11 deaths in the 32 cases (34 + per cent mortality). Even relative to ulcer of Meckel's diverticulum, with or without localized evidence of inflammation, Johnston and Renner found reported four deaths in 32 cases (12 + per cent mortality). In some reports ileal ulcer has been confused with what is now recognized as regional enteritis. Recently we have become more alert to the possibility of this nonspecific inflammatory lesion of the small bowel and as a result we have encountered an increasing number of such cases in the past three years. It is only by clinically separating these various lesions, one from the others, that diagnostic accuracy in diseases of the small bowel can be improved. Knowledge that such conditions may exist serves to stimulate development of diagnostic criteria and finally efforts toward working out of the etiology. The importance of thinking of ileal ulcer or of ulcer in Meckel's diverticulum, in contradistinction to regional enteritis, lies not so much in diagnosis as in surgery, usually, the area of enteritis is readily located whereas an ileal ulcer may be accompanied by so few signs of peritoneal involvement as to be found only by very careful exploration of the bowel.

Our study is based mainly on the surgical records of 10 patients who had solitary ulcer of the ileum and of eight patients who had ulcer of Meckel's diverticulum. There are many points common to both conditions but it is simpler to discuss them separately. In addition, we have obtained data from records of necropsy.

* Presented at the Detroit meeting of the American College of Physicians, March 2, 1936.

From the Mayo Clinic, Rochester, Minnesota.

SOLITARY ULCER OF THE ILEUM

There should be more reports on ileal ulcers than now are available. The feeling has existed that it is futile to diagnose lesions of the small bowel, and there has been a tendency to advise either to "observe further" or to "explore the small bowel." In diagnosis of chronic obstructing lesions, the roentgenologist has been of much assistance. But ileal ulcer is a clinical problem, roentgenology, as well as laboratory aids, has been chiefly of negative value in ruling out other conditions. The one exception, relative to laboratory aids, is detection of occult blood in the stool, which, if proper precautions are observed, is of real diagnostic value.

In reviewing the records of necropsy of The Mayo Clinic for the past 15 years, data were found on only one case in which death had been caused by perforation and bleeding of an ileal ulcer. This patient, a parietic, was in a hospital for the insane, and was apparently in fair physical health until he complained of vague abdominal pain which culminated abruptly, in 24 hours, with a rapidly fatal hemorrhage from the bowel. At necropsy an ulcer was found in the ileum, 80 cm from the ileocecal valve. In examination of three other subjects, who had died of debilitating or infectious diseases, a small superficial ileal ulcer was found but seemed to be only incidental. In examination of a fifth subject, who had died following ileosigmoidostomy, an ileal ulcer was found six inches (15 cm) from the ileocecal valve. This patient had been operated on in the "pre-liver days" in the hope of benefiting his pernicious anemia by excluding the colon. Apparently similar ileal ulcers, either single or multiple, have been observed occasionally in examination of subjects who had died of pernicious anemia, aplastic anemia or leukemia. The records of necropsy disclosed only one case of solitary jejunal ulcer, excluding the cases in which jejunal ulcers were associated with antecedent gastroduodenal operations. This one case was that of a patient the primary cause of whose death was Hodgkin's disease and who also suffered from psoriasis. At necropsy, a perforating jejunal ulcer was found which contributed to the final outcome. (These five cases are not included in table 1.)

Among our surgical records we have found none of a case of solitary jejunal ulcer not associated with gastric surgery. In their comprehensive review, Oudard and Jean discussed 53 cases of ulcer of the small bowel which they had collected from the foreign literature and added three of their own. They found 37 cases of solitary ileal ulcer and 19 of jejunal ulcer. Barber, in 1926, reported a case of acute perforation of a jejunal ulcer in which successful operation was performed. Other than this case, there is very little that we can find in the American literature on jejunal ulcer.

Clinical Notes. The 10 patients included in our clinical study of solitary ulcer of the ileum (table 1) consist of seven males and three females. Four of the patients were 24 to 28 years old, one, 35, three were 43, 47 and 47, respectively, and two were 58. Their symptoms covered a period of from

TABLE I
Summary of Cases of Solitary Ulcer of the Ileum

Case	Age, years, and sex	Duration of symptoms, years	Chief symptoms, site of pain	Nausea and vomiting	Stools		Blood			Preopera- tive diag- nosis	Surgical findings, type of operation and date	Pathologic examination	Result
					Tarry	Occult blood	Hemoglobin, gm per 100 c c	Erythrocytes, millions per cu mm	Leukocytes, per cu mm				
1	58 M	3	Attacks of severe epigastric pain Many mild attacks	Once	0	Test not done	*	*	*	Intestinal obstruction	Stricture lower ileum due to annu- lar constricting ulcer which caused angula- tion and obstruc- tion of ileum Lat- eral anastomosis 1917	No tissue	Well
2	58 F	18	Increasingly severe attacks of epigas- tric pain culminat- ing in constant pain in umbilical region	0	0	0	*	*	*	Chronic in- testinal ob- struction	Ulcer 3 feet from ileocecal valve pro- ducing marked dilata- tion of proximal ileum Lateral anas- tomosis 1918	No tissue	Well (?)
3	47 M	3	Attacks of severe epigastric pain, worse shortly be- fore admission Pain extended through to back	+	0	0	*	*	*	Perforated peptic ulcer	Two inches provi- mal to ileocecal valve was perfor- ated, ileal ulcer sealed off by coils of ileum Contained several ounces of thin pus Lateral anastomosis Post- operative fistula needed repair 1916	No tissue	Well

TABLE I—Continued

4	43 F	4	Attacks of severe epigastric pain and tenderness in right lower quadrant Pain extended through to back	0	+	Test not done	*	*	*	Ileocecal tumor	Ulcer in lower end of ileum causing obstruction Lateral anastomosis 1927	No tissue	Well
5	47 M	8	Tarry stools every six months Some gas and distention No pain	0	+	+	7 0	3 5	7000	Bleeding lesion of small bowel	Spleen enlarged three to four times normal Half way between duodenum and cecum, stricture due to annular ulcer Dilatation of proximal ileum Resection and anastomosis 1930	Inflammatory annular ulcer containing lymphoid tissue	Well
6	35 M	7	Attacks of sharp pain left to right at level of umbilicus Pain extended through to back Shortly before admission, weak and pale	0	+	+	7 3	3 13	6900	Bleeding lesion of small bowel	Ulcer 3 feet from ileocecal valve with dilatation of proximal ileum Resection and anastomosis 1935	Subacute simple inflammatory ulcer 1 cm in diameter	Well
7	28 M	5	Vague dyspepsia Attacks of deep, bursting pain around umbilicus Pain extended through to back	0	+	+	8 8	4 37	6200	Ileitis (?) Meckel's diverticulum (?) Duodenal ulcer (?)	Two feet proximal to ileocecal valve, angulated loop with obstruction Resection and enterostomy 1934	Annular ulcer of ileum at mouth of a Meckel's diverticulum No gastric mucosa in diverticulum	Well

TABLE I—Continued

PHILIP W. BROWN AND J. DEJ. PEMBLERTON

TABLE I—Continued

Case	Age, years, and sex	Duration of symptoms, years	Chief symptoms site of pain	Nausea and vomiting	Stools		Blood			Preoperative diagnosis	Surgical findings, type of operation and date	Pathologic examination	Result
					Tarry	Occult blood	Hemoglobin, gm per 100 c c	Erythrocytes, millions per cu mm	Leukocytes, per cu mm				
8	26 M	7/12	Attacks of abdominal pain which extended through to back Weak, pale	+	None noted	+	30	3.5	6800	Lesion of small bowel	Solitary ulcer of ileum 2 feet proximal to ileocecal valve Resection and anastomosis Spleen enlarged to two times normal 1927	Subacute simple shallow ulcer	Died third day after operation of peritonitis
9	26 M	10	Some gas Weak Pale "Catches" or pain in back, "attacks of weakness"	0	None noted	+	20	2.7	12000	Gastro-intestinal hemorrhage	Previous splenectomy of 600 gm a Meckel's diverticulum but in ileum an ulcer producing some obstruction of proximal ileum Resection and anastomosis 1930	Simple ulcer ileal mucosa in diverticulum	Well
10	24 F	10	Anemia off and on for ten years Lower abdominal cramps seven years Worse shortly before admission and associated with nausea and vomiting	+	+	7.4	3.5	4000	Lesion of small bowel Meckel's diverticulum (?)	Eighteen inches proximal to ileocecal valve was an annular stricture due to ulcer and causing obstruction Re-section and lateral anastomosis 1932	Subacute annular constricting ulcer	Died of postoperative complications, abscess with peritonitis	

* Normal

* Normal

se
ran
2,7
patie
awar
value
who ha
associat
splenic
splenect
In
data w
Surg
counce
in other
pondera
there w
the surg

seven months to 18 years with an average of more than six years. In seven cases the first symptoms were moderate to severe attacks of abdominal pain which was situated in the lower part of the epigastrium, around the umbilicus, or in the right lower quadrant. The pain was described as cramping, colicky, or as a deep, bursting pain usually accompanied by nausea and vomiting. The degree of pain eventually was found to be related to the degree of inflammation and obstruction. In five cases the pain extended into the small of the back or to the region between the shoulders. In addition to the attacks of pain, there was an irregular type of dyspepsia which had vague features of peptic ulcer, cholecystitis, or appendicitis. Taking of food sometimes initiated the distress, or again seemed to relieve it, while alkalies afforded no constant relief. One patient related that his appendix had been removed without improvement resulting. Another had undergone abdominal exploration, but the abdomen had been closed again, a report had been given the patient that there was a mass in the lower right portion of the abdomen, and anti-syphilitic treatment had been advised. A third patient said that cholecystostomy had been of no avail. A fourth, in whose case splenic anemia had been diagnosed, received no benefit from splenectomy. Of three patients, whose earlier symptoms were pallor and weakness, two had passed black, tarry stools, while the most anemic patient had not been aware of gross loss of blood from the bowel. One of these three eventually had attacks of lower abdominal cramp associated with nausea and vomiting, although the other two had only mild distention from gas, with no symptoms of moment other than the anemia.

Undoubtedly the striking symptom in six of the 10 cases was the severe secondary anemia, which was evidenced by a concentration of hemoglobin ranging from 20 to 55 per cent and a number of erythrocytes ranging from 2,700,000 to 4,370,000 per cubic millimeter of blood. The stools of all six patients were found to give a positive test for occult blood. Four had been aware of bleeding from the bowel, but of greater moment are the two, the value for whose hemoglobin was 20 per cent and 30 per cent, respectively, who had not known of any loss of blood. In examination of three patients, associated splenomegaly was found and this led to the possible diagnosis of splenic anemia, one of the patients as has been noted above, had undergone splenectomy.

In all instances, aside from anemia or blood in the stools, the laboratory data were negative.

Surgical Findings Surgery, for the type of ileal ulcer that we have encountered at the clinic, has had a more favorable outcome than that related in other reports which have been based on a series of cases in which the preponderance of ulcers has been of the perforating type. In our 10 cases, there were two postoperative deaths attributable to peritonitis secondary to the surgical difficulties but not attributable to preexisting general peritonitis. In both fatal cases, that portion of the ileum which contained the ulcer had been resected. In four of the cases in which the results were successful

resection was performed, while in the remaining four, anastomosis around the obstructed portion sufficed to effect cure. In one of the latter four cases, the patient remained well for seven or eight years, at the end of which period her physician reported that she was again suffering some abdominal difficulty, the exact nature of which is not known to us.

Notes on Pathology In nine of the ten cases the ulcer was situated from 2 to 36 inches (5 to 91 cm) proximal to the ileocecal valve. In the tenth instance it was estimated to be in the ileum about half way between the duodenum and the cecal end. In nine of the 10 cases there was more or less evidence of dilatation and thickening of the ileum proximal to the ulcer. In none of the cases was there record of enlarged lymph nodes in the mesentery. Of the six specimens available for microscopic study, three (figures 1 and 2) were described as merely "subacute simple ulcers" about 1 cm in diameter, while the other three were classified as "annular constricting ulcers" (figures 3 and 4). In one of these, much lymphoid tissue was noted but in none was any heterotopic tissue found. Evidences of tuberculosis were not found. The significance of these pathologic findings lies chiefly in the fact that it is a simple ulcer of the small bowel which may produce bleeding, perforation, or obstruction just as is true of peptic ulcer. All of the six ulcers of the patients who had been bleeding were resected, whereas in four cases the element of obstruction without demonstrated hemorrhage or anemia led to the simpler procedure of lateral anastomosis around the obstructing portion.

In two cases the ulcer was situated in the ileum, at the mouth of a Meckel's diverticulum, which raises the question if the ulcer was related to possible heterotopic mucosa in the diverticulum, such as was reported in the comprehensive study by Aschner and Karelitz. They reported two cases in which the patients were infants and found in the literature reports of 21 other cases in which gastric mucosa was present in the diverticulum, also they included 12 additional cases, in which, however, microscopic study of the diverticular mucosa had not been made. They postulated that since gastric mucosa of Meckel's diverticulum can secrete acid and ferments, stimulation of this heterotopic mucosa may be a factor in producing the ileal ulcer. In our case 7 (table 1), examination of the diverticular mucosa gave no evidence of the presence of gastric mucosa (figure 5) but only ileal mucosa. In case 9 (table 1) there was likewise only ileal mucosa, which gave evidence of chronic inflammation and subacute superficial ulceration. Although these are the only cases in our series in which Meckel's diverticulum occurred, it does seem as if the ileal ulcer was the chief lesion and the diverticulum was merely incidental. This evidence is not offered as against the possible relationship of heterotopic gastric mucosa to an ileal ulcer at the mouth of the diverticulum but merely to justify these two particular cases as examples of solitary ulcer of the ileum.

From another angle, and anticipating the second section of our paper, none of the eight patients who had inflamed, hemorrhagic Meckel's divertic-

ula had ulcer of the ileum although in five of the eight cases, gastric mucosa was found in the diverticulum. Hence, in our cases in which gastric mucosa was found in the diverticulum an ulcer had not developed in the adjacent ileal mucosa.

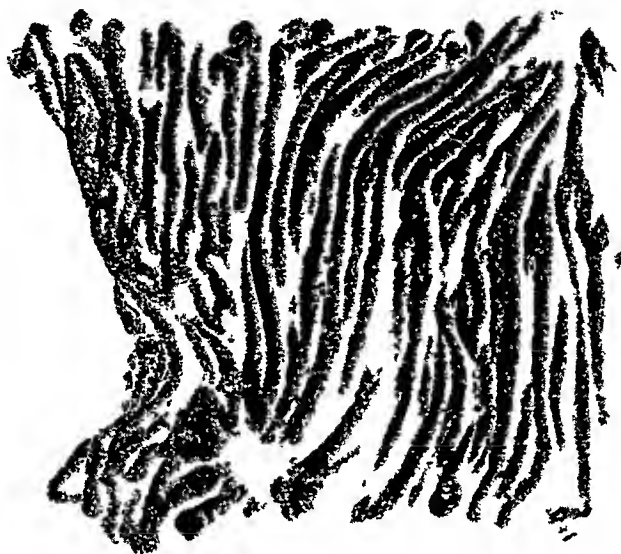


FIG 1 (Case 6, table 1) Subacute, simple ulcer of ileum, measuring 1 by 1 cm



FIG 2 (Case 8, table 1) Subacute, simple ulcer of ileum, measuring 2.5 by 1.5 cm

Comment The problem of solitary ulcer of the ileum has been tersely stated by Moiroud "Its pathology is obscure, its symptomatology is indefinite, and often perforation with peritonitis is its first revealing sign" Concerning our few cases, the last phrase could be changed to read, "and often secondary anemia with or without abdominal pain is its first revealing sign"



FIG 3 (Case 10, table 1) Subacute, constricting, annular ulcer of ileum

The various theories that have been advanced in explanation of the cause of peptic ulcer have been brought forth for solitary ileal ulcer but with no better conclusion relative to the one than to the other In 28 cases of perforated ileal ulcer, Oudard and Jean noted that six of the patients had suffered severe abdominal injury and seven had undergone severe stress just prior to the onset of symptoms No such history was obtained in our cases although there occurred no cases of acute perforation

It is strange that the lower end of the ileum is, second to the duodenum, the most vulnerable portion of the small bowel It is known that an ileal ulcer may develop when the error has been made of utilizing a loop of ileum rather than one of jejunum in the establishment of a gastro-enteric stoma Likewise, most of the Meckel's diverticula are in this last 3 feet (91 cm) of ileum All but one of 12 ileal ulcers (two seen at necropsy, not included in table 1, and 10 at operation) were found in this segment Is it possible that this portion is more vulnerable because the gradient of the entire bowel



FIG 4 (Case 10, table 1) A section of the ulcer represented in figure 3

is lowest at this point? ¹ May heterotopic tissue exist in the ileum as it does in some Meckel's diverticula? While this theory has been suggested, it does seem logical, as one would expect, that the ulcer should heal spontaneously after destruction of the heterotopic cells and that it should not persist as a chronic ulcer

--



FIG 5 (Case 7, table 1) Ulcer in ileum at mouth of a Meckel's diverticulum which contained ileal mucosa

Another query is the following Why is bleeding so common in these cases? Although ten cases are too few to permit of any conclusions, yet certainly secondary anemia was the striking symptom in two-thirds of this number Also, how can one explain the associated splenomegaly which was present in three of the six cases in which bleeding occurred and which also was noted in two of the eight cases in which there were bleeding ulcers of a Meckel's diverticulum? No patient gave any evidence of hepatic damage, nor would there seem to have been enough infection in the ulcer to produce infectious splenomegaly Dragstedt reported the case of a boy 17 years of age who was found to have an ileal ulcer at the mouth of a Meckel's diverticulum, in this case splenomegaly was noted but shortly disappeared after resection of the bleeding ulcer The patient who has secondary anemia

usually is not found to have splenomegaly although it occasionally occurs in association with the primary hypochromic anemia of women¹⁰ We have the impression that secondary anemia as a result of long-continued loss of blood from the bowel may produce splenomegaly Our data are not sufficient to support this but it may be that the size of the spleen has not been carefully noted in all cases Even though splenomegaly may occur only infrequently, it is important to bear in mind so as to avoid making a diagnosis of splenic anemia and thereby lead to splenectomy The rule of examining a series of stools for occult blood should help prevent this error Experimentally,⁷ splenomegaly has been produced as a result of chronic loss of blood from the gastrointestinal tract, myeloid metaplasia of the spleen was found to have occurred This would seem analogous to the findings in our five cases in which splenomegaly occurred

ULCER OF MECKEL'S DIVERTICULUM

The incidence of Meckel's diverticulum is about 2 per cent, with males predominating in a ratio of 2:1 The number of diverticula which produce symptoms is not easy to estimate They may be a factor in obstruction, by invagination with resulting intussusception, by producing a twist or by ensnaring a loop of bowel, especially if a remnant of the vitelline duct remains Others of these diverticula may undergo inflammatory change with resulting hemorrhage or perforation Johnston and Renner collected the data on 78 cases of this type There was microscopic proof of heterotopic mucosa in the diverticulum in 64 cases, in 50 of which definite ulceration was present In the remaining 14 cases there was gross evidence of ulcer but microscopic examination was not made Three-fourths of the 50 patients who had ulcers had suffered from bleeding from the bowel, and three-fifths of the 50 gave evidence of varying degrees of perforation

Our knowledge of this condition is again obtained from records of operation and of necropsy Data concerning the latter are not included in table 2, but from study of them Carlson has just completed a thesis on Meckel's diverticulum which covers the experience of the past 10 years His study concurs with previous reports as to the incidence of 2 per cent and as to the 2:1 ratio of males to females In 27.6 per cent of his 152 cases heterotopic tissue was found Mucosa from various parts of the gastrointestinal tract was found in any and all combinations, or identification was made of a single type of mucosa from some one part of the tract from the cardia to the colon, one diverticulum even contained only islets of Langerhans In none of the 152 cases was there evidence of ulceration, nor was the diverticulum related to the cause of death

In surgical records of the corresponding 10 years 85 cases of diverticulum were noted In 30 instances the surgeon merely recorded the abnormality as an accidental finding and the pouch was not removed In 47 of the 55 cases in which diverticula were resected, there was reason to think

TABLE II
Summary of Cases of Hemorrhagic Ulcer of Meckel's Diverticulum

Case	Age, years, and sex	Previous surgery	Duration of symptoms, years	Pain	Nausea and vomiting	Stools		Blood			Pre-operative diagnosis	Surgical treatment, date	Pathological report on diverticulum	Result
						Tarry	Occult blood	Hemoglobin, gm per 100 cc or per cent	Erythrocytes, millions per cu mm	Leukocytes, per cu mm				
1	6 M	Appendectomy, benefit	1/3	None	0	+	Test not done	12.6		8000	Meckel's diverticulum (?)	Resection for diverticulitis Enterostomosis 1933	Gastric mucosa with diverticulitis	Well
2	7 F	Appendectomy, no benefit. Resection part of ileum, no benefit	5	Attacks of diffuse abdominal pain	Not known	+	Test not done	46	3.3	8300	Meckel's diverticulum or polyp	Resection for diverticulitis 10 inches from ileocecal valve 1926	Gastric mucosa with chronic inflammation	Well
3	9 F	None	1	Severe attacks of pain lower quadrant and umbilical region	+	+	Test not done	13.7	5.38		Lesion of small bowel	Resection for diverticulitis 1930	Gastric mucosa with inflammation	Well
4	15 M	Appendectomy, benefit	12	Attacks of epigastric pain	+	+	+	66	3.69	8300	Lesion of small bowel	Resection for diverticulitis 18 inches from valve Splenomegaly (grade 1+) 1926	Diffuse diverticulitis with gastric mucosa but no acid cells	Well
5	22 M	None	9	None. Mild aching right lower quadrant	0	+	Test not done	17.2	4.94		Meckel's diverticulum	Resection for diverticulitis 36 inches from valve 1935	Ulcer at base containing polypoid gastric mucosa	Well

TABLE II—Continued

Case	Age, years, and sex	Previous surgery	Duration of symptoms, years	Pain	Nausea and vomiting	Stools		Blood			Pre- operative diag- nosis	Surgical treat- ment, date	Pathological report on diverticulum	Re- sult
						Tarry	Occult blood	Hemoglobin, gm per 100 c c or per cent	Erythrocytes, millions per cu mm	Leukocytes, per cu mm				
6	30 M	None	24	Vague symptoms of ulcer Pain right lower quad- rant three days before admission	0	+	Test not done	12.1	3.05	6400	Subacute appendicitis	Resection of ileum with marked in- flammatory di- verticular mass Appendectomy 1935	Diverticulitis of ileal mucosa	Well
7	44 J	Appendectomy and chole- cystectomy, no benefit	10½	None Vague ab- dominal distress	0	+	+	37	2.18	4000	Duodenal ulcer	Resection for di- verticulitis 24 inches from valve Spleen resected (235 gm) 1935	Jejunal mucosa	Well
8	61 M	None	10	Severe abdominal pains	+	+	Test not done	48	4.46	18500	Obstruc- tion small bowel	Entero-anastomo- sis Resection of diverticulum Much inflamma- tion (site not stated) 1930	Ileal mucosa with marked inflammation	Well

that the diverticulum might be related to the patient's complaints. These diverticula varied from the definite type, such as a large pouch filled with hard feces and impacted in the pelvis, to the smaller, more innocent appearing off-shoots, resembling segments of normal ileum, which were removed in the course of eliminating all possible sources of trouble. Kernohan, of the Section on Surgical Pathology, has studied for us this group of 47 diverticula. He reported as follows: normal ileal mucosa, 15 cases, inflammatory ileal mucosa, 22, excess lymphoid tissue in ileal mucosa, 1, excess lymphocytes in ileal mucosa, 1, gastric mucosa with acid cells, 3, and gastric mucosa (one containing carcinoma), 5.

These data would not suggest that diverticula which contain heterotopic mucosa are more likely than others to undergo inflammatory change. As previously has been noted, Carlson found 27.6 per cent of healthy heterotopic tissue in otherwise normal diverticula while in this smaller group of 47, which were removed because possibly they explained the patients' symptoms, only 16 per cent contained heterotopic tissue. Probably of considerable importance is the group of 22 patients in which varying degrees of inflammatory reaction were observed. This will constitute part of a further study in our endeavor to learn more about the symptomatology and diagnosis of diseases of the small bowel.

Clinical Notes The remaining eight cases of the 55 (table 2) are those of particular interest because they were characterized by secondary anemia and bleeding from the bowel. These are the eight cases mentioned in the introduction to this paper. Johnston and Renner found that 89 per cent of their 78 patients were 16 years of age or less. Although our group of eight cases is far too small to be comparable, yet it is of some clinical importance to note that half of the patients were more than 20 years of age (22, 30, 34, and 61 years), while the others were less than 16 years of age (15, nine, seven, and six years). The usual duration of symptoms was about the same in this group of cases as in those of ileal ulcer, ranging from four months to 24 years, although the average duration in the cases of diverticulum was higher (about nine years), the increase in the average duration is accounted for by the one patient who had some vague symptoms for 24 years but had not been ill enough to warrant operation until the recent development of more acute distress.

Bleeding from the bowel was the striking and constant finding in all eight cases, although on admission the blood count was normal in two because bleeding had not occurred for some time. Three of the eight patients made little or no complaint other than of weakness and of a history of dark to tarry stools. It will be recalled that in three of the 10 cases of ileal ulcer, anemia and weakness were the early or only symptoms of trouble.

In addition to the intestinal hemorrhages, five of the eight patients had suffered from attacks of abdominal pain. One located the pain in the epigastrium, one, across the lower part of the abdomen and around the umbilicus, and a third had pain in the right lower abdominal quadrant. In two

cases, pain was recorded only as "attacks of severe abdominal pain" In three of them, the pain was explained at operation as probably being attributable to partial obstruction, and in these cases nausea and vomiting had occurred

Results of physical examination and laboratory findings were again meager, just as in the cases of ileal ulcer In most instances, roentgenologic studies of the stomach and colon were made and, of course, abnormality was not found Examination of the blood furnished one of the two objective positive findings and in six cases revealed secondary anemia of an extent depending on how recently hemorrhage had occurred For no apparent reason the stools were examined for occult blood in only two cases and the test was positive in both

Careful study of these eight patients, together with the apparent exclusion of disease of the upper and lower ends of the digestive tube, of a splenohepatic syndrome, and of blood dyscrasia, led to a fairly accurate diagnosis of "lesion or obstruction of the small bowel" in three instances and to an even more accurate opinion in three more that a Meckel's diverticulum probably was present In case 7 (table 2) duodenal ulcer was held to be the most likely diagnosis and, in case 6 (table 2), subacute appendicitis Neither of the last two was a grave error, as it was realized that surgical indications were present It often has been emphasized that frequently it is impossible to be sure of the diagnosis, but of far greater importance is the nicety of judgment required to determine that a condition is surgical This in turn, emphasizes the responsibility of the surgeon to be prepared for, and to look for and to cope with, an unusual condition if all is not as was anticipated preoperatively

As previously has been noted, the puzzling associated splenomegaly in two of the eight cases is of much interest In one, hemorrhages had occurred 12 years prior to operation but no further gross bleeding was observed for the succeeding nine years In the other case, gross bleeding had been noted for only the eight preceding months On admission the concentration of hemoglobin was 66 per cent and 37 per cent, respectively Probably the same explanation for the splenomegaly holds in these two cases as held in the three cases of ileal ulcer in which splenomegaly occurred

Surgical Measures and Results At operation the diverticulum in four cases was 10 to 36 inches (25 to 91 cm) proximal to the ileocecal valve, in the remainder the site was not specified In all, the diverticulum was resected and the ileal defect closed In two cases, entero-anastomosis seemed advisable, for closure of the defect produced undue narrowing of the lumen No deaths occurred and these eight patients had not had further trouble at the time of writing of this paper

Notes on Pathology Microscopic study of these eight diverticula revealed the following (1) gastric mucosa with diverticulitis, (2) gastric mucosa with chronic inflammation, (3) gastric mucosa with inflammation, (4) diffuse diverticulitis with gastric mucosa but without acid cells, (5)

polypoid gastric mucosa and at its base a shallow, ulcerated area 5 mm in diameter (figure 6), (6) ileal mucosa with marked inflammation of the diverticulum, (7) jejunal tissue, and (8) diverticulitis with ileal mucosa and ulceration of the entire mucosa

Again, one is dealing with too few cases to permit conclusions, but it may be more than coincidental that five of these eight patients who suffered from intestinal hemorrhages were found to have inflammatory gastric mucosa in the diverticulum, and the diverticulum of one other contained jejunal mucosa



FIG 6 (Case 5, table 2) Meckel's diverticulum containing polypoid gastric mucosa, with ulcer at the base

SUMMARY AND CONCLUSIONS

In none of 10 cases of solitary ulcers of the ileum was there found an associated Meckel's diverticulum containing gastric mucosa which might have been a factor in producing the ulcer. Of eight cases of inflammatory, hemorrhagic ulceration of a Meckel's diverticulum, in five gastric mucosa was found in the diverticulum and in one, jejunal mucosa. Possibly heterotopic mucosa is more likely to be found in cases in which bleeding is a feature. In contrast, in 47 additional cases in which a diverticulum had been resected, bleeding did not occur and only eight diverticula were found to contain gastric tissue. In 12 of the 18 cases there were sufficient clinical data to justify a preoperative diagnosis of a lesion of the small bowel. In three others the element of obstruction was outstanding and led to a diagnosis of intestinal obstruction. In two cases the condition was mistaken for peptic ulcer and in one, for subacute appendicitis.

Although definite clinical diagnosis is impossible, yet unexplained secondary anemia associated with a history of intestinal bleeding or with blood in the stools, and associated with roentgenologic evidence of a normal stomach and colon, should arouse the suspicion that there is an ulcer in the ileum or in a Meckel's diverticulum. Although attacks of midabdominal pain are customary, yet they may not occur. These observations should be sufficient to cause the clinician to advise surgical exploration. Hence there is need of close cooperation between clinician and surgeon in order that early diagnosis may lead to prompt surgical treatment. It should not be assumed that operation is urged on the evidence of a single intestinal hemorrhage or that all patients who have unexplained secondary anemia are too hastily subjected to exploration.

TABLE III

Condensed Data Concerning 18 Cases in Which Hemorrhagic, Ulcerative Lesions of the Ileum Existed

	Sex		Age, years	Pain	History of intestinal hemorrhage	Anemia	Occult blood in stool	Splenomegaly	Surgical result	
	Male	Female							Cured	Died
Solitary ulcer of the ileum (10 cases)	7	3	24 to 58	8	4	6	6*	3	8	2
Ulcer of Meckel's diverticulum (8 cases)	5	3	6 to 61	5	8	6	2†	2	8	

* No test made in two cases

† No test made in six cases

Pictures (table 3) of the two hemorrhagic, ulcerative lesions of the ileum which are the subject of this paper, represented by our 18 cases, may be described as follows:

Solitary Ulcer of the Ileum Usually the patient is an adult aged 20 to 60 years, of either sex but more likely a male, who gives a history of having had attacks of abdominal pain for about six years. This pain is situated in the region of the umbilicus and often extends through to the small of the back or to the region between the shoulders. The patient usually is pale and although he may have been aware of intestinal hemorrhages, this is not always so, possibly because of minute, steady bleeding, lack of observation, or color blindness. Studies of the stomach, duodenum, colon, and liver are normal. The blood count may be normal but often discloses secondary anemia. The examining physician should exercise care not to be misled by the finding of an enlarged spleen. The test for occult blood in the stool is usually positive. Less often, the syndrome presented by a male, who has

secondary anemia, who has no abdominal distress, and all studies of whom give negative results, except for a positive test for blood in the stool, should suggest ileal ulcer

Ulcer of Meckel's Diverticulum The same general picture applies except that the age level is lower and that among children this condition rather than ileal ulcer is more likely to be the cause of tarry stools and anemia

BIBLIOGRAPHY

- 1 ALVARO, W C The mechanics of the digestive tract, 1922, P B Hoeber, New York, 192 pp
- 2 ASCHNER, P W, and KARLITZ, S Peptic ulcer of Meckel's diverticulum and ileum, Ann Surg, 1930, xci, 573-582
- 3 BARBER, W H Ulcer of the jejunum, Ann Surg, 1926, lxxiv, 621-623
- 4 CARLSON, L A Unpublished data
- 5 DRACSTEDT, L R Ulcus acidum of Meckel's diverticulum, Jr Am Med Assoc, 1933, ci, 20-22
- 6 JOHNSTON, L B, and RENNEL, G Peptic ulcer of Meckel's diverticulum, Surg, Gynec and Obst, 1934, lxx, 198-209
- 7 LANGE, F J Myeloid metaplasia, Folia haemat, 1930, xliii, 95-120
- 8 MOIROUD, P Perforation d'un ulcere simple de l'ileon, Bull et mem Soc nat de chir, 1932, lvi, 1157-1162
- 9 OUDARD and JEAN, G L'ulcere simple du grele, Arch d mal de l'app digestif, 1925, xv, 208-228
- 10 WITTS, L J Simple achilohydric anemia, Guy's Hosp Rep, 1930, lxxx, 253-296

ERRORS IN THE INTERPRETATION OF CARDIO-VASCULAR SYMPTOMS AND SIGNS ¹

By PAUL D. WHITE, M.D., F.A.C.P., *Boston, Massachusetts*

ERRORS often lead the way to new knowledge. Some of the most important advances in medicine have developed from the recognition and study of errors. Many details of our present rapidly progressing understanding of the diagnosis of cardiovascular disease have arisen from our analysis of errors in the interpretation of cardiovascular symptoms and signs. It is of some of these that I shall speak to you today.

The appraisal of cardiac symptoms, the most important part of cardiovascular examination and the part that requires no use of hands or instruments, is, and always has been, the most imperfect and neglected. Why this is so is strange, but it is a fact which cannot be overemphasized in the present state of medical training and practice. Too often the history of the patient is relegated to a relatively untrained person when it would be safer to turn over any other part of the examination. Or the physician is too hurried, or tired, or preoccupied to do a proper job. In ancient days the presentation of symptoms was usually too brief, leaving out important clues, in recent years there has been a tendency to bury the clues in a mass of details which are often irrelevant. The chronological development and relationships of the chief symptoms are the essentials which with past and family history permit in most cases a correct diagnosis of the cardiovascular condition, even before the physical examination is begun. I shall first present errors in the interpretation of the three chief cardiac symptoms—pain, dyspnea, and palpitation.

A. SYMPTOMS

1. Pain

Mrs. E. C. M., 54 years old, housewife, entered the Massachusetts General Hospital on April 5, 1933, to have treatment for persistently recurring nocturnal heart attacks by paravertebral alcohol injection of the sympathetic nerve ganglia and ramus.

Five years before she had begun to be troubled by momentary attacks of sharp, shooting pain originating just over the heart to the left of the sternum and radiating across the chest to the right and occasionally up over the left chest, almost to the clavicle. These transitory pains were not associated with exertion but seemed to come more when she was resting after a hard day and in the evening when in bed. She consulted her doctor who gave her tablets of nitroglycerine for the attacks, which seemed to give relief. This was at the time of the menopause. Ever since then this trouble had recurred at intervals, more frequently during the few weeks prior to her admission to the hospital, when she also noticed almost constant heartache, some dyspnea on hurrying, and blueness of her fingers and lips. Her ankles seemed to swell slightly at the end of the day. Her doctor digitalized her but she said that she had to omit the drug because of her inability to retain it.

* Read at the Detroit meeting of the American College of Physicians March 3, 1936.

About one year before entrance to the hospital she was troubled by another and more important symptom, consisting of precordial and substernal oppression in attacks at night awakening her and causing her to sit up, lasting for a few minutes at a time, and not responding quickly to nitroglycerine. On one occasion she was given morphine for relief. During the three weeks before entrance to the hospital these nocturnal attacks had increased in frequency and severity, and had been accompanied by a feeling of impending death, cold sweat, and rapid heart beat. She had, however, continued to do her housework as before.

Her past history revealed no important illnesses. She had six healthy children. Her mother and one sister had died of tuberculosis.

Physical examination showed a well developed and well nourished middle-aged woman with good color, normal breathing, no edema, and no abnormal neck pulsations. Her heart was normal in size, sounds, rate, and rhythm. There were no murmurs. The pulse rate was 80. The blood pressure varied from 154 to 165 millimeters of mercury systolic and from 90 to 100 diastolic. The lungs were normal.

Electrocardiogram showed normal rhythm and total inversion of Lead III.

Roentgen-ray examination showed some increase in the transverse diameter of the heart, which was recorded as greater than the long diameter.

The urine and blood were normal except for very slight albuminuria and slight secondary anemia. There was no bile in the urine. The stool was normal. The Hinton reaction was negative and the basal metabolic rate was minus 10 per cent.

On April 5, the day of her admission to the hospital, I saw her for a few minutes and wrote the following opinion: "Brief questioning does indicate the apparent occurrence of severe angina pectoris (decubitus) dating back three weeks (mild for two or three years before that). Examination shows no abnormalities except for slight hypertension. Further study—more careful history, electrocardiogram, roentgen-ray, Hinton reaction—are essential before final diagnosis. Paravertebral alcohol injection may well be indicated but I would advise postponing it for a few days until studies are completed. Try amyl nitrite for attacks." The surgeon wrote the following note in the record: "I believe that this patient is a suitable case for paravertebral alcohol block as her cardiac pain is so severe and she is getting so little relief from her medical measures. The only difficulty is the bilateral nature of the pain."

On April 7, 1933, we questioned her more carefully, realizing how rare severe angina pectoris is in a middle-aged woman with little or no hypertension and no story of substernal oppression on effort, and we gave the following verdict: "Further history this morning reveals the vitally important fact that rapid regular heart beating at more than twice the usual speed always accompanies the anterior chest discomfort and apparently precedes it. *This is extremely significant for it changes the diagnosis from coronary disease with angina pectoris to paroxysmal tachycardia with little or no heart disease.* She is already better in here resting. Sedatives and quinine sulphate (3 grams three times daily) will be much more likely to help her than any other drugs. I expect the Hinton reaction will be negative. For completeness we shall have a basal metabolic rate determination. Certainly there is no need at present for paravertebral alcohol injection unless the paroxysms grow very much worse and are refractory." One week later on the new therapy she was feeling very well, completely free of heart attacks. She was discharged from the hospital much improved on April 15.

Three months later, on July 3, 1933, she came to my office with no complaints except for very slight heart twinges for a second at a time on two days the previous week. She was taking quinine. Examination including electrocardiogram and fluoroscopy showed nothing amiss except for slight hypertension (170 mm systolic and 95 diastolic).

In October she reported the occurrence of a spell of racing of the heart lasting

a half hour after a recent fatiguing day. She had omitted the quinidine but thereupon resumed it. She no longer was afraid of the attacks—they had become simply disagreeable. Her blood pressure was 155 systolic and 90 diastolic.

I have continued to see this patient at intervals ever since, the last time on February 10, 1936, three weeks ago. She continued in good health (with infrequent palpitation) except for a series of acute attacks of typical gall stone colic with vomiting from August to November of last year (1935), completely relieved by the uneventful removal of her gall-bladder containing a large stone. She continued to have infrequent brief paroxysms of tachycardia up to the time of operation but none in the three months thereafter. The blood pressure continued to be slightly elevated (170 systolic and 95 diastolic on February 10, 1936). The electrocardiogram, including the chest lead, has been normal.

There are several morals to this tale. The most important one, of course, is the establishment by careful history taking of the correct diagnosis whereby the patient was not tagged with the label of a serious ailment and unnecessarily treated therefore. It is by no means the first time that such an error has occurred, I myself have encountered several other cases, the last one only a few weeks ago. The most notable patient of the sort that I recall was Jonnesco's first special case of supposed angina pectoris submitted to cervical sympathectomy who was still alive and in a good state of health many years afterwards, a review of the history of that case establishes this point*. There the history was all right but its interpretation was in error.

A second point of importance in this case is the change in the patient's reaction to the paroxysms of tachycardia. In a person untrained medically the first paroxysm of tachycardia usually causes great fear and discomfort, sometimes this happens even in a doctor. At such a critical time, or soon after, if a physician pronounces a verdict of heart disease and especially of angina pectoris, and warns against exertion and prescribes nitroglycerine, it is a very easy matter for the patient to develop a cardiac neurosis superimposed on the paroxysmal tachycardia. The palpitation due to the tachycardia becomes more disagreeable and in a nervously sensitive person even painful. The constant repetition causes a great dread and finally there is the addition of the fear of impending death and of a cold sweat at the time of the paroxysm, and of neurocirculatory asthemia with dyspnea and constant heartache and disturbed peripheral circulation between attacks, as in my case. When the patient is reassured and loses her fear of the attacks, only the disagreeable palpitation remains, and the fear of impending death and the cold sweat and other symptoms vanish. So it is, too, sometimes in the case of angina pectoris, although the more severe nature of this ailment more often justifies and causes these additional symptoms. As a matter of fact the great majority of my cases of angina pectoris have had neither the sense of impending dissolution nor cold sweating.

Here I would add an aside, namely, that there are cases of paroxysmal tachycardia or paroxysmal auricular fibrillation with coronary disease who

* JONNESCO, T. *Le sympathique cervico-thoracique*, Masson et Cie, Paris, 1923.

do have real angina pectoris (a sort of status anginosus) during their rapid heart beating, but such patients are usually seriously crippled by angina pectoris on effort to start with. They are generally benefited by quinidine therapy but they live short lives after the beginning of such a history. The patient whose story I have recounted was not one of these.

There is a third point of interest. My patient for some years had temporary flashes of precordial pain when quiet, beginning at the time of her menopause. Such pain is almost always an excessive reaction of a nervously sensitive patient to an extrasystole. In such a case there is often tenderness on palpation of the precordium. Apparently in patients who have had painful reactions to paroxysmal tachycardia there may be developed a conditioned reflex to tachycardia that isn't even paroxysmal, that is, to a slight elevation of the heart rate of 20 or 30 or 40 beats, a sinusoidal tachycardia due to excitement or effort, so that even the rehearsal of the "sad story of illness" may precipitate one of these heart attacks, accompanied sometimes by tears.

A fourth point of importance is the patient's reaction to therapy. Quinidine was almost a specific, and it may very well be that some of the cases labeled angina pectoris who have been benefited by quinidine have had either painful sensations due to premature beats or paroxysmal tachycardia which have been controlled by the drug and which have been wrongly interpreted as angina pectoris due to coronary disease. In our case nitroglycerine was thought to have helped the transient pains but not the more prolonged heart attacks, it may conceivably have acted a little like exercise or atropine by raising the intrinsic heart rate and so abolishing extrasystoles. Digitalis, on the other hand, usually aggravates the uncomfortable symptoms produced by extrasystoles or paroxysmal tachycardia and may cause these disturbances of rhythm in the first place, as it did in myself experimentally twenty years ago.

The variations from the usual normal findings in the electrocardiogram and roentgen-ray picture in this patient of mine tended at first to cause further suspicion of heart disease. I shall mention them simply because they too are morals in this particular tale. Both the total inversion of Lead III and the reversed relationship of the measurements of the transverse and long diameters are unimportant findings in an individual who is fat, whose diaphragm is high, and whose heart lies horizontally, as in my case. Often in such cases the inclusion in the measurement of two or three centimeters of a triangular shadow of pericardial fat at the cardiac apex adds to the gross error.

The last point I would mention in my case is the possible relationship of the gall stone to the heart attacks. In the first place the stone did not cause the precordial distress although such a site of gall-bladder pain can occur, as I have recently experienced regretfully in a case wrongly diagnosed coronary thrombosis. When in my patient whose history I recounted above the gall stone did cause pain, that pain was upper abdominal and associated with vomiting. However, it is conceivable that the paroxysmal tachycardia

may have been a reflex manifestation of the gall stone or it may have been a reflex from something else if it was a reflex at all. At any rate it was not evidence of any rapidly progressive heart disease.

Before leaving the subject of heart pain I shall simply recount the 28 conditions mentioned by Dr. James Herrick, in a paper last year,² that he has himself found to have been confused with coronary thrombosis, which as we all know has recently been considerably overdiagnosed: paroxysmal angina pectoris, cardiac arrhythmias, cardiac neuroses, neurocirculatory asthenia, malingering, acute pericarditis, luetic aortitis with or without aneurysm, dissecting aortic aneurysm, pleurisy, pneumonia, carcinoma of bronchus or lung, massive collapse of the lung, pneumothorax, pulmonary embolism, herpes zoster, arthritis of costochondral articulation, shoulders, or spine, bursitis, gall stones, peptic ulcer, carcinoma of stomach or duodenum, acute gastritis, spastic colitis, diaphragmatic hernia, tabetic crisis, and impending diabetic coma.

2 Dyspnea is often misinterpreted. The common breathlessness of neurocirculatory asthenia in a nervously tired person or in one who is "soft" and physically unfit has been often treated as cardiac dyspnea with restriction in exercise and with digitalis therapy, when almost the opposite measures are indicated. A careful history should at once correct this error of interpretation and treatment with the support of the finding on examination of no reason or evidence of myocardial weakness. The most common error in this respect is to be misled by the dyspnea of neurocirculatory asthenia when there is also present actual organic heart disease without failure. Long experience and good judgment are sometimes essential in the proper analysis of such a case. An extremely helpful clue when present is sighing respiration, which is never primarily due to heart disease. A patient who comes into your office and seats herself with a sigh saying "Well, here I am, doctor" reveals at least part of the diagnosis in the first few seconds of her interview.

Dyspnea of pulmonary origin is less commonly confused with cardiac dyspnea, but the error is often enough made to warrant much care in analysis. Chronic bronchitis with emphysema and weakness of the left ventricle with pulmonary vascular congestion and emphysema are the two conditions which in an elderly person, especially in the winter, are likely to be mistaken for each other. And sometimes they are actually superimposed. The history of respiratory infection, the presence of heart disease, roentgen-ray evidence, and the quick response to adequate digitalis therapy are the important clues, by their proper use the differential diagnosis is generally easy.

It should be observed that a chronic as well as an acute asthmatic state may be caused by congestion of the lungs secondary to heart disease. This is not widely appreciated.

One important error of interpretation that used to be made frequently but which is now uncommon is illustrated by the following case. A man 55

* Jr. Med. Soc. New Jersey, Oct., 1935, XXXII, 590.

years old is awakened at night by a severe pain in the epigastrium and lower anterior part of the chest. He gets up, takes hot water and soda bicarbonate, and belches gas. After a half hour without relief a doctor is called. He gives morphine subcutaneously with slight relief. A half hour later the patient vomits several times. Another hypodermic injection of morphine is given for the persistent pain which finally dies away after some twelve hours. The next evening the patient is wheezy and coughs a little. He prefers to sit up in bed. His lungs show scattered râles and emphysematous breathing. He may become definitely and even seriously asthmatic. His temperature is 101 degrees.

Both doctor and patient may be content with the one time "obvious" diagnosis of acute indigestion complicated by bronchitis or bronchiopneumonia with asthma, but careful analysis and experience suggest the true diagnosis of coronary thrombosis with myocardial infarction followed by left ventricular dilatation with failure and acute pulmonary edema, the electrocardiogram will confirm the suspicion of coronary thrombosis in nearly every case. It is the morphine in such patients that may be wholly or at least in part responsible for the vomiting.

When there is marked mitral stenosis the most common symptom is dyspnea on effort, or in attacks (with or without asthma) or constantly. Such dyspnea is certainly to be ascribed to pulmonary vascular engorgement with too little room for air, as is evident by roentgen-ray examination and in fatal cases by autopsy finding of the marked engorgement of even the lung capillaries. But, granted all this, it is still the rule wrongly to attribute this dyspnea to heart, or rather myocardial, failure. To be sure, the dyspnea and pulmonary engorgement are due to the heart disease but they aren't due to myocardial failure. Rather the reverse. Actually the left ventricle is small, under no strain, not dilated, and not failing. The right ventricle is large and strong and also not failing, provided there is no increase in systemic venous pressure (as shown by normal neck veins, non-engorged liver, and no dependent edema). The answer is to be found in the disproportion between the strength and activity of the right ventricle and the narrow size of the mitral valve ostium. More blood is pumped into the lungs and left auricle in a given unit of time than can pass through the mitral valve—it is a mere matter of mechanics. It is thus obvious that digitalis will not help in such a case *unless it will reduce the heart rate* and thereby decrease the blood flow into the lungs. Fortunately in most cases of the sort digitalis does that very thing and hence is helpful. This is true in practically all cases of auricular fibrillation where the ventricular rate is at first rapid and uncontrolled. It is sometimes even true when the rhythm is normal, but far less frequently. At least the drug should always be tried. The slower the pulse rate in such cases the less the pulmonary congestion, and any measures besides digitalis that keep the heart from beating fast should be utilized.

There is one more important point concerning dyspnea that I shall mention. A good many individuals with heart disease and weakness are

troubled by insomnia. Very often this insomnia is frankly due to nervousness and very often to orthopnea secondary to pulmonary congestion, but there are borderline cases, and nervousness alone should not be blamed for the insomnia and treated as such, until the situation has been carefully analyzed. Digitalis and diuretic drugs may prove to be specific remedies for the insomnia in such patients.

3 **Palpitation** is due to the consciousness of forceful, rapid, or irregular heart action. It is never in itself a sign of heart disease and should never be prognosed and treated as such until the patient has been carefully studied. It may initiate a cardiac neurosis or even neurocirculatory asthenia unless properly handled at the outset. The most common condition associated with palpitation, that is more than the simple awareness of extrasystoles or short paroxysms of tachycardia, is neurocirculatory asthenia, of which it is frequently the chief symptom. Much has been written of the chance of confusing thyrotoxicosis, with its frequently disturbed heart rhythm and palpitation, with heart disease, but not so much has been said of confusing neurocirculatory asthenia with thyrotoxicosis. I shall recount briefly such a case.

An athletic young man, 20 years old, had a gruelling experience during the World War in 1918 and developed palpitation with a rather rapid pulse, nervousness, insomnia, exhaustion, and a precordial aching with a little dyspnea. When the war was over he rested and gradually recovered good health but three years later while studying hard in law he had a return of these same symptoms along with a feeling of tightness of the collar. Although worried about his health for a long time then, he did not consult a doctor because he was afraid that a serious diagnosis would be made. Finally after a year or two he did go to a physician who told him that he had an "athletic heart," and prescribed digitalis and bromide, the former drug did not help him, the latter did. Still not feeling well he consulted another doctor who made the diagnosis of thyrotoxicosis. Medical treatment of the condition seemed ineffective and finally partial thyroidectomy was done, at first he felt somewhat better but while still convalescent he had a year of heavy strain looking after his sick mother and later after his sick sister. Feeling poorly, with a return of all his old symptoms he consulted more doctors who suspected tuberculosis and advised treatment therefor which was carried out for a brief time. Then he returned to hard work with intense nervous strain and tried to save money on which to marry. He would return home exhausted every evening, but he continued to work hard and to worry about his work and his finances. His symptoms increased. He became panicky and finally consulted a doctor once more. Recurrent thyrotoxicosis was diagnosed and a second thyroidectomy was done four years after the first. Two months after the operation he felt somewhat improved and was married. His home life was very happy and his wife was sympathetic. His mental strain decreased and he no longer feared death, but he has never felt strong since this second operation. In a few years he began to feel nervously tense again, all his old symptoms recurred. Thyrotoxicosis was suspected once more but his basal metabolic rate was normal.

On examination last year I found this man, then 37 years old, to outward appearance in good health, very alert and breathing normally except for an occasional sigh. His reflexes were exaggerated. The thyroid gland was not enlarged, the neck showed an excellent scar. There was no abnormal pulse in the neck. The heart was normal in size, sounds, and rhythm. There were no murmurs. There was no evi-

dence of congestive failure. The pulse was regular at 120. The blood pressure was 145 systolic and 100 diastolic. Fluoroscopy showed a normally shaped, though unusually active, heart; a normal aorta, and normal lungs. Electrocardiography showed sinoauricular tachycardia with normal chest lead.

This man has improved in the past year on vigorous reassurance, regular exercise, ample rest, restricted work, omission of tea and coffee, small amounts of alcohol and tobacco, and the occasional use of bromides. It is obvious that his diagnosis is now and quite probably always has been, neurocirculatory asthemia, whatever that is, and not thyrotoxicosis, tuberculosis or heart disease. Cases somewhat like his are very common though not always so striking.

B. SIGNS. I shall now very briefly present a few cases illustrating common errors in the interpretation of cardiovascular signs.

1. Cardiac Enlargement. It is quite a common error for an over-active heart to be misjudged in size, especially by an inexperienced observer. The forceful apex impulse produces a widespread movement of the anterior chest wall which may be seen and felt several centimeters beyond the cardiac apex itself. If the outermost point of this impulse vibration is taken as the left edge of the heart, and especially if the measurement is made following the curve of the chest rather than tangentially from the midsternal line, a gross and misleading error results. The maximal point of the apex impulse is to be taken as the position of the cardiac apex itself, using the much neglected and sometimes scorned but nevertheless valuable method of percussion for control, at least until a roentgen-ray examination is available.

It is a less common error to underestimate the heart size. There are to be sure still a few individuals who speak of normal heart size when the maximal apex impulse and left border of dullness are located in the left nipple line but fortunately their number is steadily decreasing. Rarely the nipple line may be near enough to the sternum to be the proper position for the left edge of a heart of normal size but almost always it is one to two centimeters too far to the left, the so-called midclavicular line should be used as a guide.

On a few occasions it is possible to misjudge the heart size grossly on hasty examination when a fairly forceful impulse is felt near or in the midclavicular line in patients with mitral valve disease whose hearts are very large and whose powerful right ventricles may displace the anterior chest wall while the true apex impulse is in or near the left anterior axillary line. I have recently made this error twice in the same patient whom I examined in April 1934 and again in December 1935—I had forgotten the first error. This was the case of a young woman with mitral stenosis and auricular fibrillation and a very large heart. It is of considerable interest and importance in such cases to observe that the characteristic diastolic murmur of mitral stenosis is often and in fact usually limited to the immediate vicinity of the true apex impulse in the axilla, if cardiac auscultation is not carried out to that region the diagnosis of mitral stenosis may be missed. And again I would urge that careful percussion be also done in the third left inter-space to detect marked increase in size of the infundibulum of the right

ventricle and prominence of the root of the pulmonary artery, particularly in cases with suspected mitral stenosis

2 Now a few words about **heart murmurs** I shall limit my remarks to two particular murmurs and I shall give two cases in illustration

(a) A boy, eight years old, is seen in the third month of his first attack of rheumatic fever. He is still moderately ill with a slight elevation of temperature in the afternoon, occasional mild rheumatic pains and nose-bleeds, malaise and slight leukocytosis. He had a pericardial friction rub for a few days a month ago. Observation shows a pale listless child lying in bed in no discomfort. No abnormalities are found on examination except for a regular rapid heart action of 120, a moderately enlarged heart, and blowing systolic and rumbling mid-diastolic murmurs at the cardiac apex. There are no thrills. There is no evidence of congestive failure in lungs, liver, neck or dependent parts of the body. The diagnosis is made of subacute rheumatic infection, rheumatic heart disease, and mitral stenosis and regurgitation. He is thought to show early mitral valve disease with deformity, including stenosis.

An acute exacerbation of the rheumatic infection occurs and the boy dies four months after trouble started. Autopsy shows no deformity of any heart valve, but an enlarged dilated heart with myocardial rheumatic lesions (Aschoff bodies), small vegetations on the line of closure of the mitral valve, and acute fibrinous pericarditis.

Having been caught like this on a good many cases over a period of 10 years Dr Bland, Dr Jones, and I a few years ago began to suspect the truth and gradually assembled data which we published in the December 1935, number of the *American Heart Journal*. We believe that this paper is a very important one. The moral to the tale is that during a severe infection, especially rheumatic fever which attacks the myocardium, dilatation of the left ventricle may give rise to a mitral diastolic murmur (and in some cases even an accompanying thrill) which we used to think was pathognomonic of mitral stenosis, in the absence of free aortic regurgitation producing the so-called Austin Flint murmur. I believe that the murmur is due to the relative mitral stenosis (dilated left ventricular cavity and undeformed mitral valve) whether there is any aortic regurgitation or not. In the series of cases to which I am referring now particularly there was no aortic regurgitation. Hence when during acute or subacute rheumatic infection a mitral diastolic murmur is found to appear in the course of weeks or months it should be interpreted as I have done above and not considered to be evidence of real mitral stenosis, if it was heard before the infection or if there was a previous rheumatic infection some years earlier, then we are dealing with another matter and quite likely do have a mitral valve deformity with stenosis. It is important to remember that from this study close to two years must elapse after the beginning of a rheumatic infection of the heart before there is an appreciable stenosis of the mitral valve. Patients showing the mitral diastolic murmur due to left ventricular dilatation during acute or subacute rheumatism may die or they may recover—it is an important sign of myocardial infection and weakness. Those cases that recover may show a gradual transition in a period of years to true mitral stenosis, but sometimes they lose their murmurs altogether. When the mitral diastolic mur-

mur disappears with recovery we must not say that we are mistaken ever to have heard the murmur, nor can we say that valvular disease and deformity have been cured (as has sometimes been declared erroneously)

Parenthetically it may be added that other diseases besides acute rheumatic infection may cause temporary mitral diastolic murmurs as the result of left ventricular dilatation, this is especially the case in severe anemia due to any cause

(b) A physician, 53 years old, consulted me in September 1926, because on a recent life insurance examination a systolic heart murmur had been found and he had been passed only with a higher age rating. He felt perfectly well but wanted me to tell him the significance of the murmur. He was a very healthy appearing, heavy man with good color and normal breathing. The only abnormalities were slight cardiac enlargement, a moderately loud blowing systolic murmur widely heard all over the precordium but maximal at the apex, without palpable thrill, and with a few premature beats. The blood pressure was 140 millimeters systolic and 90 diastolic. Electrocardiogram showed slight left axis deviation. I made a diagnosis of cardiac enlargement and mitral regurgitation, of unknown cause. He was advised to lose weight, to avoid fatigue, and to report for annual examinations. Lost to sight for nine years, he consulted us again last fall because of a history of attacks of acute pulmonary edema at night following a few months of rather poor health with dyspnea on effort after a grippe attack last spring. He was found in serious congestive failure. His heart was somewhat more enlarged than it was nine years earlier, the loud systolic murmur was much as before but more intense and as loud at the aortic valve area as at the apex, and now an aortic systolic thrill was easily felt. The aortic second sound was audible but less loud than an accentuated pulmonary second sound. The diagnosis of aortic stenosis was now evident with congestive failure therefrom.

The aortic stenosis was undoubtedly the cause of the widespread loud systolic murmur heard nine years before. The diagnosis was missed then, but now that we have had such experiences repeatedly we are becoming wiser and making the correct diagnosis earlier, before all the so-called classical signs appear. The etiology of the aortic stenosis in this case is in doubt as it is in many other patients. Rheumatic infection is obviously the cause in some and probably it is in a good many others, infection in middle aged men may be the cause in a few. Calcification often found is probably nearly always a complication, usually appearing late in advanced cases, and not itself the only cause of marked aortic stenosis. It should be possible to diagnose aortic stenosis by physical examination before there is enough calcification to show well by roentgen-ray study—the roentgen-ray diagnosis can be made only in advanced cases.

3 Finally, I shall have a word to say about errors in the interpretation of congestion including dropsy.

A married mill worker, 30 years old, mother of one child, was referred to me in January 1933, because of persistent dropsy. For two and one half years she had had gradually increasing anasarca, which had failed to yield to medical treatment consisting of rest, digitalis, and diuretic drugs. Several doctors had diagnosed heart disease and congestive failure. My examination revealed a slender woman with

marked edema of both legs extending to the hips and up to the waist with some fluid in the peritoneal and right pleural cavities, some engorgement of the neck veins with venous pressure of 16 centimeters, small regular pulse of 84 with blood pressure of 105 millimeters systolic and 70 diastolic, and heart normal in size with good sounds and no murmurs. Electrocardiogram showed low voltage of QRS and T-waves in all leads. Roentgen-ray examination revealed normal sized heart and aorta with little or no pulsation of right border but active pulsation of the left and upward displacement of the left leaf of the diaphragm with systole. These findings established the diagnosis of chronic constrictive pericarditis, and the operation of pericardial resection was carried out by Dr. Churchill in April 1933. A spontaneous diuresis began three days after the operation and within one month the dropsy had completely vanished with a loss of twenty and one-half pounds. She has been in excellent health ever since, having resumed work in the mill.

Here is an example of venous congestion due not to heart disease and failure but to the mechanical interference of a thick callous constricting pericardium. The same effect is produced by marked tricuspid stenosis in rare cases. Comparably, as I have already said, when there is pulmonary vascular congestion in marked mitral stenosis, it is not primarily myocardial failure that is responsible, but the mechanical influence of the valvular defect. This viewpoint is of great importance in the proper understanding and treatment of vascular congestion not due to myocardial failure.

I have herewith presented a number of cardiovascular symptoms and signs that are likely to be misinterpreted. Through our diagnostic errors in the past, caused by such misinterpretation, important advances have been made. We should search diligently for more errors in the future for there is still a great deal for us to learn therefrom.

THE INITIAL VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM IN CORONARY THROMBOSIS¹

By L. FELDMAN, M.D. *Chicago, Illinois*

THE changes in the final ventricular complex, the T-wave, and in the S-T segment of the electrocardiogram in coronary thrombosis have been extensively studied, both experimentally and clinically, since the early works of Herrick,¹ Smith,² and Pardee.³ As a result, it has been generally accepted that characteristic changes do occur in the majority of the cases, following an attack of coronary thrombosis.

In contrast, the changes in the initial ventricular complex have, up to recent years, received much less attention. Smith² and Weain⁴ observed that in coronary thrombosis the initial ventricular complex may not rarely be of a very small amplitude. The former observed such a reduction of the amplitude following coronary ligation in animals. Oppenheimer and Rothschild⁵ found arborization block in a number of their cases of coronary thrombosis that were studied postmortem. Various grades of intraventricular conduction disturbances have been reported to have appeared following coronary thrombosis.

That Q may become prominent in myocardial infarction was first observed by Pardee,⁶ and later by Wilson,⁷ Parkinson and Bedford,⁸ and by Levine.⁹ Fenchel and Kugel¹⁰ suggested that a large Q in coronary thrombosis was probably due to involvement of the posterior portion of the ventricular septum, and that large Q deflections in other leads may have a similar clinical significance.

On the other hand, many articles^{11, 12, 13, 14} have appeared showing that a large Q₁ may also be encountered in such conditions as coronary sclerosis, hypertension, obesity, pregnancy, rheumatic heart disease (without right axis deviation), and not rarely as a variation of the normal electrocardiogram. Wilson¹⁵ and his associates recently described certain changes in the initial deflection of the ventricular complex in association with coronary thrombosis. They classified these changes as belonging to Q₁ and Q₂ groups. The former was most frequently observed in association with the T₁ type of electrocardiogram, and the latter with the T₂ type, as classified by Parkinson and Bedford.⁸

The Q₁ group is characterized by "the presence of a conspicuous and, in most instances, rather broad Q in Lead I, the absence of Q in Leads II and III, the small amplitude of the largest of the initial deflections in Lead I, and the presence of a conspicuous S in Leads II and III. In some instances

* Received for publication January 14, 1936.

From the Department of Medicine, Mount Sinai Hospital, Chicago, Illinois.

one or more of these characteristics may be absent or poorly developed. Nevertheless, all of these curves display a family resemblance.

The Q_3 group is characterized by "the absence of Q in Lead I, the presence of a conspicuous Q in Leads II and III, and relatively small amplitude of the initial ventricular deflection in Lead II." Here, too, the authors stress the fact that not all curves show all the characteristics mentioned. They add "Curves in which Q is absent in Lead II, as well as in Lead I, and in which T is inverted in Lead III only, are not infrequent in myocardial infarction, they are not rare, however, in young individuals in whom there is no reason to suspect cardiac disease."

The absence of characteristic changes in the S-T segments or in the T-waves in some of the authors' curves is attributed by them to the long interval that elapsed between the occurrence of the infarction and the recording of the tracings.

Winternitz¹⁶ described changes in the initial ventricular complex of the electrocardiogram in coronary thrombosis. His first group is not unlike the Q_1 group of Wilson¹⁵. His second group is characterized by negativity of the principal deflections in all leads. The amplitude is low and the main deflection may be Q or S . His third group is typified by intraventricular conduction disturbance, resembling arborization block.

Barnes¹⁷ studied a group of cases and he found that coronary thrombosis is frequently followed by electrocardiographic changes that conform to the Q and T patterns. He concluded that the combined consideration of the changes in the initial and in the final ventricular complex yields more information regarding coronary thrombosis than does the study of either change alone.

Durant¹⁸ studied 74 cases of coronary thrombosis, and he found that 38 cases (51.3 per cent) showed changes in the initial ventricular complex of either Q_1 or Q_3 types. He concluded that the relative permanence of these changes greatly enhances their value in the recognition of old myocardial infarcts.

Since various conditions, such as rheumatic fever, pericarditis, coronary sclerosis, anoxemia, large fatigued hearts, digitalis, uremia, pneumonia, etc., are known to produce changes in the S-T segment and in the T-wave very much akin to those seen in coronary thrombosis, the uncovering, by the authors mentioned above, of changes in the initial ventricular complex that may be produced by the latter condition should be of great value.

MATERIAL STUDIED

One hundred and eight electrocardiograms of patients with coronary thrombosis were reviewed. The diagnoses were based on good clinical evidence. Service cases had the opinions of the attending staff, and private cases had frequently the opinion of a cardiac consultant, although characteristic changes in the electrocardiogram, when they occurred, were taken

into consideration in reaching a decision. In most instances the patient was seen and an electrocardiogram taken some hours or days after the onset of symptoms. Only very few patients were seen weeks after, unless they experienced a new attack before completely recovering from the first. Very frequently the tracing was repeated in a few days, less frequently was a third one taken, and in practically none was a serial study made. Of the 34 patients that died, eight were studied postmortem.

Eleven electrocardiograms showed no changes of any kind. Forty-five cases displayed various changes in the S-T interval and in the T-wave significant of coronary thrombosis, but had no changes in the initial ventricular deflection. Fifty-one cases exhibited Q patterns associated with T-changes. There was one case which showed a marked left axis deviation with a good-sized Q_1 , without changes, recent or old, in the final ventricular complex. She died soon after admission, no autopsy was obtained. Twelve cases showed extremely low Q-R-S complexes.

CURVES OF THE Q_1 GROUP

Using the criteria of Wilson¹¹ and his associates, we classified 19 cases as belonging to the Q_1 group. Almost all of these had in association changes of the T_1 type. The six curves in figure 1 represent the typical changes and the variations of this group, showing that the family resemblance prevails.¹⁵

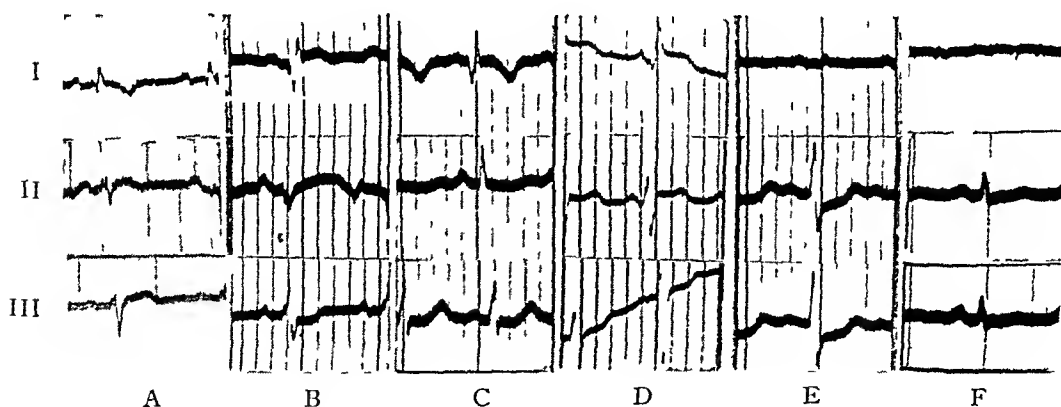


FIG 1 Electrocardiograms of six patients displaying initial ventricular deflections of the Q_1 type

Figure 1A typifies this group. There is a conspicuous Q in Lead I. In Leads II and III the first ventricular deflection is upward and is followed by a deep S-wave. The initial deflections are small in Lead I. T_1 is sharply inverted, and the S-T₁ and S-T₃ intervals are elevated and rounded. The patient was a man 40 years old who had a typical attack three weeks before the tracing was taken. He recovered.

Curve 1B was taken three days after the attack in a man 56 years old,

who nine months previously was seen with a severe attack of coronary thrombosis. He survived the second attack, dying suddenly two months later. This curve is similar in general outline to that shown above, although it differs from the latter in some detail, the amplitudes of the initial deflections in Lead I are comparatively large, S_2 is comparatively small, and S_2 is widened and rather inconspicuous. $S-T_1$ is elevated, $S-T_2$ is elevated and rounded, giving a monophasic curve, and $S-T_3$ is depressed. It is possible in this case that the somewhat atypical changes in the initial ventricular complex may be due to the ancient infarction. That the Q may persist for such a length of time following the attack was stressed by Wilson.¹⁵

Tracing 1C is also quite different in detail from the typical. While Q_1 is prominent, R_1 is quite large. S_2 is lacking and S_3 is small. T_1 is sharply inverted, and $S-T_2$ interval is slightly depressed. This tracing was taken seven weeks after the attack in a man 57 years old. He recovered. The time interval, here too, is probably responsible for the variation, for the tracing is more characteristic of an old infarct than of a fresh one.

Figure 1D is that of a man 59 years old, taken four days after the onset of an attack, and one day before his death. Except for a large R_1 it is typical of the group under consideration. There is also intraventricular conduction disturbance. The changes in the $S-T$ intervals are highly significant of coronary thrombosis in the acute phase.

Curve 1E represents still another variation of this family group. The very low amplitude of the initial ventricular deflections and the conspicuous S_2 and S_3 qualify this electrocardiogram for the Q_1 group, in spite of the absence of Q_1 . The absence of the latter is probably due to the low voltage in Lead I. The $S-T$ intervals are not markedly altered, probably due to the time interval since the attack, which happened three weeks previously. This was a woman 59 years old, dying the day after the tracing was taken. This curve is similar to that shown by Wilson¹⁶ (see his figure 8) which is of a man 44 years old, with coronary thrombosis. Autopsy showed occlusion of the anterior descending branch of the left coronary artery. The infarcts invaded the anterior and lateral walls of the left ventricle.

Tracing 1F is also slightly different from the typical in this group. The very small Q in Lead I, the small S in Lead III and the inconspicuous S in Lead II are all probably due to the low voltage. $S-T_1$ is altered, while the final complexes in the other leads show no conspicuous changes. It is a tracing of a man of 60, one week after the onset. He recovered.

Except for the duration of Q_1 and its relative amplitude in comparison with the succeeding upstroke, the initial ventricular deflections of some of the curves typical of this group are very similar to those of left axis deviation, due to preponderate hypertrophy of the left ventricle (figures 1A and 1D). It is also possible that left ventricular hypertrophy, which is common in patients of the class subject to coronary thrombosis, may have played a part in determining the form of the initial ventricular deflections, especially large S_2 and S_3 . Wilson,¹ however, shows that myocardial infarction may

produce such curves. He cites a case (see his figure 4) having an electrocardiogram taken before and after the attack of coronary thrombosis. The latter showed the development of large S_1 and S_2 , and a very small initial deflection in Lead I. Q_1 is not definite but suggestive. He cites another similar case (see his figure 5), thus proving that infarction may produce such changes in the form of the initial ventricular complexes.

CURVES OF THE Q_1 GROUP

Twenty records were classified into the Q_1 group, all of which were associated with T_1 type changes. The six curves in figure 2 are representatives of this class.

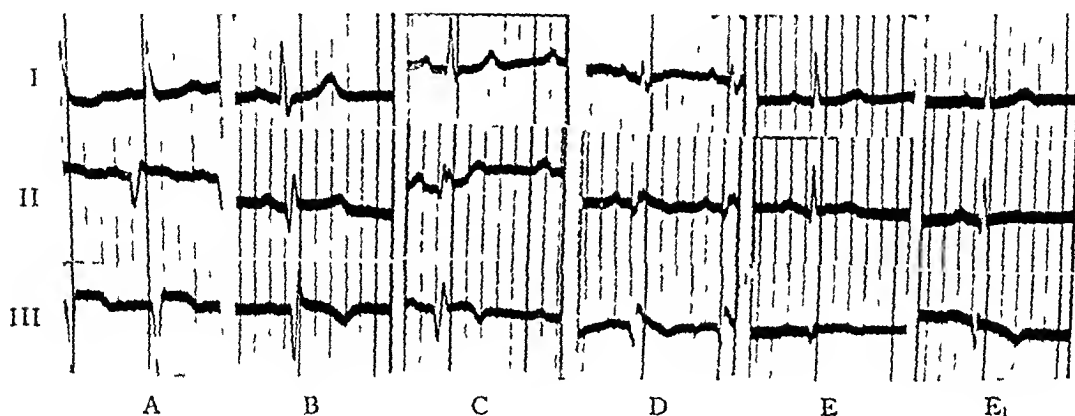


FIG 2 Electrocardiograms of five patients showing initial ventricular deflections of the Q_1 type. Tracings E and E_1 are of one patient, taken three days apart.

Figure 2A is typical of this type of curve. The characteristic features are: absence of Q in Lead I, the presence of a conspicuous Q in Leads II and III, and the relatively small amplitude of the initial ventricular deflections in Lead II. In Lead III, Q is often the largest and, at times, the only initial deflection. It is a tracing of a man of 58 years, taken two days after the attack, from which he survived. There are definite S-T and T changes of the T_1 type.

Curve 2B is that of a man 43 years old, taken two days after the attack, from which he recovered. The curve is similar to the previous one, with the exception of a conspicuous R in Leads II and III. The changes in the final ventricular complex are those of type T_2 .

Tracing 2C is of a man 63 years old, one day after the attack. The Q in Lead II is not as prominent as in the previous curves, but the amplitude of the initial ventricular deflections is more typical. The R in Lead II is quite notched. The S-T and T changes are characteristic of the T_2 type. The patient improved, but continued to show marked myocardial insufficiency.

Figure 2D is a typical tracing of the group under consideration. It is of a man 67 years old, four days after the attack and one day before death.

There is also evidence of intraventricular conduction disturbance, and the changes in the final complex are those of an acute phase of infarction.

Curves 2E and 2F are of one patient, a man 48 years old. The former was taken two days following the attack. This curve is not typical of the class under discussion. The Q_2 is small, R_2 quite large, and Q_3 very small. The S-T intervals show only slight changes. The latter curve was taken three days later and five days following the attack, Q_3 has become prominent, T_3 more inverted, and T_2 flattened. The initial ventricular complexes in the other leads did not change. This curve is an example of the appearance of a large Q_1 and inverted T_3 following coronary thrombosis.

Curves of this description are not rare in coronary thrombosis^{6, 7, 8, 9}. There were 12 other such curves in our 108 records. However, as mentioned above, they may also be seen in conditions other than coronary thrombosis^{11, 12, 13, 14, 15}.

PERSISTENCE OF QRS CHANGES

Since our cases were seen mostly days after the infarction, the persistence of the changes in the initial ventricular complexes could not be studied. Those cases seen by us weeks after the attack and a few, months after, were again in the throes of a new attack on admission, thus precluding any conclusions. Wilson¹⁵ and his associates express the opinion that the changes in the initial ventricular complex of the types described are often more persistent than the characteristic changes in the final deflection of the ventricular complex, and that they may be helpful in recognizing an old myocardial infarction. They cite a case in whom Q_2 and Q_3 were present five and one-half months after the infarction, while the T reverted to normal long before.

Wallace¹⁹ cites a case showing persistent Q_1 and Q_2 almost one year after the acute attack of coronary thrombosis and months after the changes in the final ventricular complex had disappeared.

CORRELATION WITH POSTMORTEM FINDINGS

Wilson¹⁵ and his associates, in discussing the correlation of the Q_1 and Q_3 type of electrocardiogram with the location of the infarct, concluded that while infarction in the anterior wall of the left ventricle and the adjacent septum was generally associated with ventricular complexes of the Q_1 - T_1 type, it may be accompanied by curves of the Q_2 - T_2 type, or possibly by no definite electrocardiographic changes of any kind. They also found instances both in their own series and in those reported in the literature, where curves of the Q_1 - T_1 type were produced by infarction of the posterior wall of the left ventricle.

Barnes,²⁰ in correlating the changes in the initial ventricular deflections with the site of the myocardial infarct, concludes that tracings typical of the Q_1 - T_1 group are found to be associated with infarction of the anterior wall of the left ventricle and the adjacent septum. Infarction of the posterior

wall of the left ventricle and the adjacent septum is accompanied by curves of the Q_3 - T_3 group

Eight cases of our series were autopsied. The location of the infarcts and the changes in the coronary arteries were carefully studied by Dr. I. Davidsohn, with the following results:

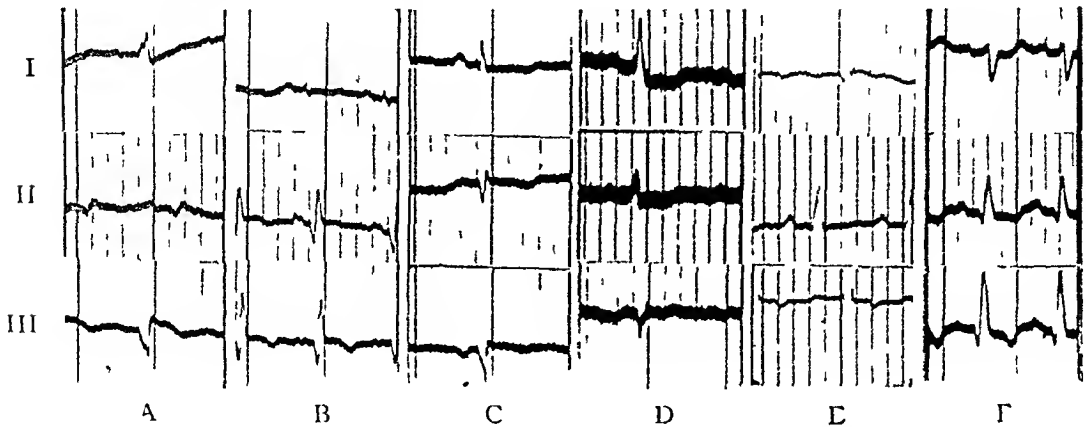


FIG. 3. Electrocardiograms of six patients that were studied postmortem.

Figure 3A is that of a man 68 years old, who died one week after the attack. It belongs to the Q_3 - T_3 group. The opening of the right coronary artery was completely occluded by a thrombus. The left coronary artery showed a moderate degree of sclerosis. Acute myomalacia of the posterior wall of the left ventricle and the posterior half of the septum was found. There were pericardial adhesions posteriorly.

Figure 3B is that of a woman 69 years old, who died three weeks after the attack. The tracing was taken one week after the onset, and it belongs to the Q_3 - T_3 type. There was a complete occlusion of the left circumflex artery, with myomalacia of the posterior wall of the left ventricle and, to a lesser degree, of the posterior half of the septum.

Figure 3C. This was a man 45 years old. The tracing belongs to the Q_3 group. The first attack came six weeks prior, and the second two days before the tracing was taken. He died two days later. There was occlusion of the entire descending branch of the left coronary artery, with an aneurysm of the left ventricle at the apex. There was also recent thrombosis of the right coronary artery near its mouth, with acute myomalacia of the posterior wall of the left ventricle, right ventricle, and the posterior half of the septum. T_1 is diphasic, T_2 is inverted, and S - T_3 is elevated. The changes in the initial ventricular complex fit in with posterior infarction, while the changes in T_1 and T_2 may be remnants of the anterior infarction.

Figure 3D is a tracing of a man 57 years old, one week after the attack. He gave no history of any previous attacks. There is only Q_3 present, which is slurred and atypical. There is depression of all the S - T segments. He died two weeks later. There was an obliterating thrombosis of the

anterior descending branch of the left coronary artery, with an aneurysm of the left ventricle at the apex. More recent thrombosis of the right coronary artery near its orifice with acute myomalacia of the posterior wall of the left ventricle was also present. The more recent infarction possibly is responsible for the Q_3 (Fenichel and Kugel¹⁰), while the diphasic T-waves may be a vestige of the older damage.

Figure 3E. A woman 62 years old. The tracing was taken two weeks after the attack. She died three weeks later. There is a small Q_1 and a deep Q_2 . The changes in the final ventricular complex are not readily discernible. There was a thrombosis of the left descending coronary artery and of the circumflex branch, also acute myomalacia of the anterior wall of the ventricle, and, to a lesser extent, on the posterior wall.

Figure 3F is a tracing of a woman 50 years old. She had severe nocturnal dyspnea with collapse two weeks before the tracing was recorded. Death occurred three weeks after the onset. The electrocardiogram shows right axis deviation with conspicuous Q_1 , T_1 and T_2 are inverted. There was a thrombosis of the first part of the anterior descending branch and of the circumflex branch of the left coronary artery. There was also an occlusion of the right coronary artery 3 cm from its origin. Fairly recent myomalacia of the apex, the adjacent septum, the posterior wall of the left ventricle, and the posterior half of the septum resulted.

Figure 4D is a tracing of a man 60 years old, taken three days after the attack. He died three weeks later. The tracing does not belong to either of the groups under consideration. The changes in the final ventricular complex are significant, but not typical of any particular type. There was thrombosis of the circumflex branch of the left coronary artery, with acute myomalacia of the posterior wall of the left ventricle.

Figure 4E. A man 61 years old. The tracing was taken three days after the attack and two days before death. Except for the low amplitude and slurring, there are no significant changes in the initial ventricular complex. The T changes are of the T_1 type. There was a thrombosis of the circumflex branch of the left coronary artery, atheromatous changes in the descending branch of the left coronary artery, and also in the right coronary artery. Early myomalacia of the posterior wall of the left ventricle resulted.

Hence, four cases showing infarction of the posterior wall of the left ventricle had tracings of the Q_2 - T_2 type. In two cases having both anterior and posterior infarctions the electrocardiograms did not conform to any type. However, the right axis deviation in one of them (figure 3F) is rather significant. One case of posterior infarction failed to show changes conforming to either the Q_1 or Q_3 type. Finally, the last case of posterior infarction showed typical T changes, the initial ventricular complex was of low amplitude and markedly slurred, but without any Q waves.

OTHER CHANGES IN THE INITIAL VENTRICULAR COMPLEX

There were 12 cases in our series showing extremely low initial ventricular complexes. These changes, helpful in the diagnosis of coronary thrombosis, were described previously^{4,5,10}. The first three tracings in figure 4 represent such changes.

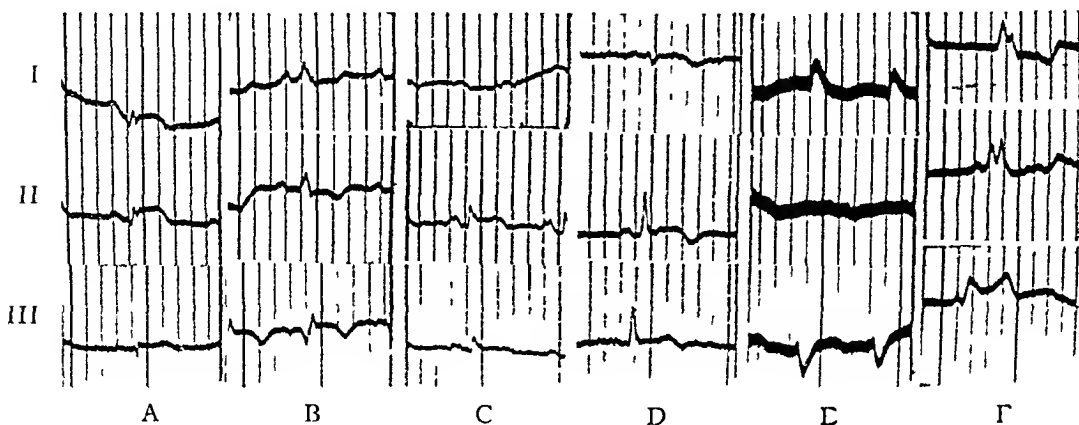


FIG. 4. Electrocardiograms of six patients. A, B, C, and D display low amplitude of the QRS deflections. D and E were studied postmortem, and F shows bundle branch block.

Figure 4A is that of a man 42 years old, taken three days after an attack. The S-T and T changes are not unlike those described by Barnes²¹ as occurring in coronary thrombosis complicated by pericarditis. The patient recovered.

Figure 4B. This is the tracing of a man 67 years old, taken three weeks following an attack and three days before death. The curve conforms to the Q_s - T_s type.

Figure 4C is that of a man 60 years old, taken six days after the attack. He improved.

Figure 4F shows bundle branch block of the common variety. We had six such tracings in our series. This patient was 69 years old. The tracing was taken 10 days following the attack, and one week before death. Such changes in conduction are helpful in the diagnosis of coronary thrombosis^{5,15}.

SUMMARY

One hundred and eight electrocardiograms of patients with coronary thrombosis were studied with particular reference to the changes in the initial ventricular complexes.

Eleven tracings showed no changes in either the initial or the final ventricular complexes.

Forty-five cases showed changes in the final ventricular complex (S-T and T-waves) only.

Fifty-one records (47.22 per cent) displayed conspicuous Q-waves in association with characteristic changes in the S-T segments and T-waves.

Nineteen of these, belonging to the Q_1 group and almost always associated with the final ventricular deflection of the T_1 type, displayed often a conspicuous Q-wave in Lead I, while the other Q-R-S deflections in this lead were small. In Leads II and III, the first deflection of the ventricular complex is upward and is often followed by a large S deflection. However, Q_1 may be very large and S_2 and S_3 may be small or absent.

Twenty tracings of the 51 were classified into the Q_3 group and were accompanied by the final ventricular deflection of the T_3 type. The characteristics are usually a large Q-wave in Leads II and III, but no Q in Lead I. There is frequently a relatively small amplitude of the initial ventricular deflections in Lead II.

There were twelve curves showing Q- T_3 only. In one case this finding was inconspicuous two days after the attack, only to become prominent three days later.

Since various other conditions may be associated with changes in the S-T segments and T-waves, the presence also of changes in the initial ventricular complex is of additional value in the diagnosis of coronary thrombosis.

Changes in the initial ventricular complex without accompanying changes in the final ventricular complex are rare in acute coronary thrombosis. Such a curve would speak, instead, for an old infarction.

Most of the cases that had posterior infarctions showed tracings of the Q_3 - T_3 type, while the rest, either having multiple infarctions or a single posterior one, displayed curves that did not conform to either Q_1 or Q_3 groups. The number of autopsies being small, no definite conclusions can be drawn.

Other changes in the initial ventricular complex, such as marked reduction in amplitude, or the development of intraventricular conduction disturbances, may occur in coronary thrombosis.

REFERENCES

1. HERRICK, J. B. Thrombosis of the coronary arteries, *Jr Am Med Assoc*, 1919, **lxvii**, 387.
2. SMITH, F. M. Ligation of coronary arteries with electrocardiographic studies, *Arch Int Med*, 1918, **xxii**, 8.
3. PARDEE, H. E. B. An electrocardiographic sign of coronary artery obstruction, *Arch Int Med*, 1920, **xxvi**, 244.
4. WEARN, J. T. Thrombosis of coronary arteries, *Am Jr Med Sci*, 1923, **clxv**, 250.
5. OPPENHEIMER and ROTHCHILD. Electrocardiographic changes associated with myocardial involvement, *Jr Am Med Assoc*, 1917, **lxix**, 429.
6. PARDEE, H. E. B. Clinical aspects of the electrocardiogram, First Ed., 1924, Paul B. Hoeber, Inc., N. Y., p. 82.
7. WILSON, W. J. Cardiac clinic with electrocardiographic demonstrations, *Ann Clin Med*, 1926, **v**, 238.
8. PARKINSON, J., and BEDFORD, D. E. Successive changes in the electrocardiogram after cardiac infarction, *Heart*, 1928, **xiv**, 195.

- 9 LEVINE, S. A. Coronary thrombosis—its various clinical features, *Medicine*, 1929, viii, 245
- 10 FENICHEL, N. M., and KUGEL, V. H. The large Q-wave in the electrocardiogram, a correlation with pathological observation, *Am Heart Jr*, 1931, vii, 234
- 11 STRAUSS, S., and FIDMAN, L. The significance of the large Q in Lead III, *Am Jr Med Sci*, 1933, lxxv, 87
- 12 EDEKIN and WOLFEH. Incidence and significance of deep Q in Lead III, *Am Heart Jr*, 1932, vii, 695
- 13 ZISKIN, T. Clinical significance of the electrocardiogram with large Q in Lead III, *Arch Int Med*, 1932, l, 435
- 14 FELDMAN, L., and HILL, H. The electrocardiogram of the normal heart in pregnancy, *Am Heart Jr*, 1934, x, 110
- 15 WILSON, F. N., MACLEOD, A. G., BARKER, P. S., JOHNSTON, F. D., and KLOSTERMAN, L. L. The electrocardiogram in myocardial infarction with particular reference to the initial deflection of the ventricular complex, *Heart*, 1933, xvi, 155
- 16 WINTERNITZ, M. The initial complex of the electrocardiogram after infarction of the human heart, *Am Heart Jr*, 1934, ix, 616
- 17 BARNES, A. R. Q and T types of electrocardiograms, their comparative and complementary value in indicating occurrence of acute myocardial infarction, *Am Heart Jr*, 1934, ix, 722
- 18 DURANT, T. M. The initial ventricular deflection of the electrocardiogram in coronary disease, *Am Jr Med Sci*, 1934, clxxviii, 225
- 19 WALLACE, A. W. The Q-wave in the electrocardiogram, *Am Jr Med Sci*, 1934, clxxviii, 498
- 20 BARNES, A. R. Correlation of initial ventricular complex with situation of acute myocardial infarction, *Am Heart Jr*, 1934, ix, 728
- 21 BARNES, A. R. Electrocardiographic pattern observed, following coronary occlusion, complicated by pericarditis, *Am Heart Jr*, 1934, ix, 734

LATE RECRUDESCENCE IN ENCEPHALITIS LE- THARGICA WITH SUCCESSION OF NEW MANIFESTATIONS AT INTERVALS OF YEARS, THE PROBLEM OF PROGNOSIS *

By ALFRED GORDON, F A C P , *Philadelphia, Pennsylvania*

It is pretty well established that the virus of encephalitis lethargica may invade any area of the central nervous system but has a special affinity for the striatal region in the mid-brain. The Parkinsonian symptom-group is the usual clinical expression of this localization. As to the so-called sequelae, the literature shows a multiplicity of phenomena. The sensory system, the special sense organs, the motor system, the vegetative nervous system, the psychic functions—all may show morbid alterations. Some of these various manifestations are rare or very rare, while others are common. Hyperkinetic phenomena are the most frequent. Since, in some cases, the postencephalitic sequelae are chronologically not far distant from the original malady, and since usually when they do occur, they remain fixed, it might seem a logical deduction that the pathological substratum, which is directly responsible, is fixed and shows no tendency to extension and further involvement. On the other hand there are cases in which aggravation of the preexisting symptoms occurs and also the appearance of new manifestations. Such observations, of course, can only signify a progressive and extensive development of the original lesions, due in all probability to the persistence of the encephalitic virus in the nervous tissue. The clinical histories of many such cases indicate that the virus may remain active in the nervous tissue for a considerable time, that it is capable of causing new anatomical lesions and extensions of preexisting ones. They also indicate that there is no certainty as to whether the virus is ever completely eliminated, and if its elimination is possible, within what period of time it may be accomplished. It is uncertain also, should the virus be eliminated, whether the lesions can regress, and to what extent and with how much consequent amelioration of the clinical manifestations. Our present therapeutic resources do not include any method of neutralizing the virus in order to obtain a regression of the anatomical lesions and consequently a modification in the course of the syndrome. The postencephalitic manifestations should not be considered merely as sequelae, but as forms of a genuine chronic evolution in the presence of a virus which is still active.

The present contribution has for object to put on record additional data demonstrating the grave possibility that the apparent subsidence of an encephalitic invasion does not necessarily indicate a finished process, and that

* Received for publication September 27, 1935

Patients presented before the Philadelphia Neurological Society

the virus may exist in a latent state even for many years, during which the clinical manifestations remain unaltered and fixed. Recrudescences may develop, not only after the acute state, but also many years later, and new phenomena may appear in the domain of extrapyramidal, pyramidal, bulbar and cerebellar domains, or at any level of the central nervous system. The succession of pathological manifestations in the same individual at intervals of years demonstrates the fact that the so-called sequelae are not of evolutionary character, but late and definite reactivations of the original infectious process, especially characteristic of lethargic encephalitis. These observations have a very considerable and serious bearing on the prognosis in this grave affection. They prove that it would be erroneous to assume a final position as to the course of lethargic encephalitis even after the Parkinsonian syndrome became definite. Besides the main object of this presentation, namely to suggest the importance of a reserved prognosis, attention is also called to some new and unusual features which have not yet been recorded in the literature as very late occurrences in lethargic encephalitis of long standing.

CASE REPORTS

Case 1 M. P., a newspaper dealer, 35 years old, 15 years earlier had a condition characterized by sudden onset, somnolence, fever, and double vision. He was bed-ridden for four weeks. He then presented the attitude general fixation, facies and fine tremor of the hands and lips, characteristic of the Parkinsonian syndrome following an acute attack of encephalitis lethargica. The condition remained unaltered for six years, when he developed the oculogyric manifestations from which he is still suffering. The eyes roll up suddenly and may remain in that position for between one and 10 hours. An emotional upset may precipitate an attack, but emotion is not the exclusive exciting factor. Physical fatigue may do likewise. On the other hand the upward deviation of the eyes may occur even after a good rest or early in the morning, before he commences to work. Sometimes the attack occurs while the patient is in his conveyance, distributing papers. The patient is absolutely unable to overcome this condition. All possible efforts on his part to bring the eyes down are futile. In his work he is obliged to be accompanied by someone as he is unable to continue his work and cannot walk by himself while the eyes are in the upward position. Seven months ago, that is over 14 years after the acute attack, he developed another additional disorder. Almost at every meal, while masticating his food, there occurs a sudden rigidity and immobility of the tongue, and the patient is unable to roll the food from side to side. This may last as long as five or ten minutes. These paroxysms have been quite frequent of late. Three months ago he developed another additional symptom, namely sudden closure of his eyes which, like the other symptom, may set in without warning. Any effort on his part to reopen the eyes is useless. This manifestation lasts a shorter time than the upward movements of the eyes, but, like the latter, it equally incapacitates him and interrupts his work.

The previous medical history of the patient is essentially negative. Lues is improbable since the Wassermann reaction of blood and spinal fluid is negative. Urinalysis is negative. Eye grounds are intact. There is no organic involvement of the ocular muscles. The circulatory system is normal. The reflexes, sensations, pupillary reactions are all intact. There are no pathological reflexes.

To sum up, we are dealing with a typical case of Parkinsonian syndrome subsequent to an attack of lethargic encephalitis 15 years earlier. Since

then, at different periods up to the present and at intervals of years between each other, the patient has developed three different phenomena, namely six years after the onset of encephalitis, the oculogyric phenomena, five years still later, the attacks of rigidity and immobility of the tongue, and much later (about three months ago) attacks of uncontrollable closure of the eyelids with hypertonicity of the orbicularis palpebrarum muscles

Case 2 S S, girl, 20 years of age, seven years ago developed a typical attack of lethargic encephalitis (somnia and fever). Shortly afterwards she observed a stiffness of the jaw and later an impediment of speech. The condition progressed for a time and then remained stationary. The speech disorder presented certain unusual features. Briefly, while speaking the tongue protrudes between the teeth, rolls curls and moves to the right side, at the same time two deep furrows appear on both sides of her mouth. (For details of this unusual postencephalitic manifestation, the reader is referred to the *ANNALS OF INTERNAL MEDICINE*, 1933, vi, 895.) There is no evidence of aphasia, paraphasia, or anarthria. Because of the dysfunction of the tongue, the food remains in the mouth a long while, and there is also pronounced salivation. The palate and pharynx are intact. Simultaneously with the speech-disorder appeared myoclonic contractions of the muscles of the left hand, so that the fingers would flex and extend alternately. Somewhat later a tremor was observed in the same hand. During a period of four years this speech manifestation and the tremor of the left hand were the only postencephalitic sequelae. At the end of the fourth year the patient began to observe a gradually oncoming weakness of the right upper extremity. At that time both knee-jerks were increased, but there were no other pathological reflexes. One year ago, that is six years after the acute attack, for the first time she noticed a tendency to turn her head to the left. This condition gradually increased in frequency and intensity so that, at present, a typical spasmodic torticollis is established. The former paretic condition of the right arm has greatly increased within one year, so that she is compelled to use her left hand almost exclusively. Moreover, the right leg, in addition to the increased knee-jerk, presents now an extensor plantar reflex, a condition which was not present two years ago. A general somatic examination is essentially negative. Blood, spinal fluid, urine, show no special disorder worth mentioning. The mental state is normal.

To sum up, the following course of events has been observed in a period of seven years. At first a typical picture of encephalitis lethargica. Shortly after the acute period, there developed an unusual speech disorder which persists at present, also myoclonia and tremor of the left hand. The next abnormal symptom (four years later) was a paretic state of the right arm which progressively increased. Next, in the chronological disorder (in the fifth year), was the extensor plantar reflex on the right side and finally a progressive spasmodic torticollis became established. The clinical symptoms, therefore, indicate an involvement of the extrapyramidal and pyramidal systems. The speech disorder, with particular disturbance of the function of the tongue in the act of speaking, may be the result of a nuclear involvement in the medulla or rather of an interruption in the structural connection of the striatum with the important bulbar segments of the central nervous system.

Hypertonia or dystonia and hyperkinesia are met with frequently in the postencephalitic period. The muscular phenomena may be generalized or

limited to circumscribed areas. They may be due to an irregular muscular function confined to the peripheral agencies. An improper and abnormal use of the many small muscles which enter into the formation of syllables and words in speech, and therefore in the enunciation of words, may be the cause of the speech disorder. The hyperkinesia in the form of the torticollis is another clinical evidence of a new invasion of the striatal connections.

In this case, as in the first, we observed several encephalitic sequelae, developing at very long intervals between each other, demonstrating the existence of latent or silent periods of years' duration after the acute attack of infection. Therefore a final fixed stage in the disease under discussion is not admissible.

CONCLUSION

Two cases are reported which are instructive from the standpoint of prognosis in encephalitis lethargica. Even years after the onset of this disease recrudescences may occur attacking any part of the central nervous system. The so-called sequelae are an indication of chronicity of the pathological processes and persistence of the virus.

CASE REPORTS

RENAL DWARFISM, A CASE REPORT

By J F ROBERTS, M D, *Toronto, Canada*

THE relationship between chronic interstitial nephritis in childhood and the occurrence of infantilism, late rickets, and dwarfism as sequelae, was first clearly defined by Fletcher¹ in 1911. Thirty years previously Lucas² had noted the frequent association of albuminuria with late rickets but had regarded the albuminuria as functional. Renal dwarfism, however, has only been recognized as a definite clinical entity since 1920, when Barber³ introduced the name, and defined it as "a condition of stunted development, associated with bone deformities of the 'late' rickets type, due to an insidious chronic interstitial nephritis of obscure etiology." The terms, renal dwarfism, renal infantilism, and renal rickets have been variously used for this group of cases, depending on whether dwarfism, infantilism or rickets was the predominating clinical feature. At present there are about one hundred examples of this condition recorded.

Attention has recently been drawn, by Ellis and Evans,⁴ to the importance and frequency of other abnormalities occurring in the urinary tract in this condition, namely, hypertrophy of bladder and dilatation of ureters and kidney pelvises, without any malformation or lesion to account for the obvious obstruction. In their report of 20 cases which came to postmortem, 14 showed these changes, but no organic lesion was found, and the author suggested a disorder of the neuro-muscular mechanism controlling the urethro-vesical sphincter, as the responsible factor.

More recently Ellis⁵ has reported a case with similar dilatation of the urinary tract, in which a definite organic obstruction of the nature of a valve in the posterior urethra was found, to account for the back pressure.

The following case report has a threefold purpose, first, to report a case of renal dwarfism, second, to call further attention to the association of this syndrome with an unexplained dilatation of the urinary tract, as described by Ellis and Evans, in contrast to that reported by Ellis, and, third, to direct attention to changes in the pituitary gland with a view to their possible bearing on the development of the dwarfism.

CASE REPORT

D K, a male, first came under observation at the Hospital for Sick Children in May 1926 at the age of eight years, with symptoms of cystitis and pyelitis of two weeks' duration, and a history of polydipsia and polyuria dating from 12 months of age, excessive in character both day and night. At birth he was normal in size and development. At four years he had measles and at six, whooping cough.

* Received for publication October 3, 1935.

From the Department of Pathology, University of Toronto.

On examination he was described as poorly developed and emaciated with normal intelligence, an irritable cough and slight naso-pharyngitis. The bladder was distended to the umbilicus. The urine showed 1+ albumin and a specific gravity of 1.002 on three examinations. Pus and *B. coli* were identified. Blood examination showed hemoglobin 65 per cent, red blood cells 3,900,000, white blood cells 34,000. Differential count 82 per cent polymorphonuclears and 18 per cent lymphocytes. He was discharged one week later, much improved.

The next note was that at the age of 13 years and again about one year later at 14 he had attacks of short duration, described as cystitis.

He was finally admitted to the Toronto General Hospital in December 1934, at 16 years of age because of difficulty in breathing of two days' duration. History obtained from relatives at this time stated that for the past two months it had been noticed that he appeared tired all the time and drowsy. This was sufficiently marked to keep him from school, for the first time. He complained of cramps in his legs, numbness of his hands and after laying down objects held by the fingers, they would stay "flexed" for a short time. For the past month he had had a head cold, a non-productive cough and considerable nasal discharge. Since one year of age he had drunk large quantities of water and passed large quantities of urine throughout the same interval. For the week prior to admission his polydipsia had markedly decreased. The breathing difficulty began two days ago and his physician took swabs and administered 60,000 units of diphtheria antitoxin. The swabs were negative.

It is noted that this boy began school at eight years, was quite bright as a student never missing an examination. He played with, and acted like, boys of his own age, but he has not grown for the last seven years. The family history was negative. On examination he was described as a small red haired boy appearing of about half the stated age, conscious, very hoarse, breathing with considerable difficulty. The respirations were rapid and stertorous, with prolonged expiration. Râles were heard in both lungs. Examinations of the heart and of the abdomen were essentially negative. The external genitalia were undeveloped, with no pubic hair, and the testicles undescended. The nervous system was negative. No urine could be obtained. The blood showed a hemoglobin of 70 per cent, red blood cells 4,200,000, white blood cells 24,000. Non-protein nitrogen, 111 mg per cent. CO_2 combining power 10 per cent, fasting blood sugar 0.07 per cent, serum SN P 2+. The Wassermann was not taken. The patient died in a generalized convulsion shortly after admission to hospital, before further examination could be carried out.

Summary of Postmortem Findings. Symmetrical dwarfed male of juvenile appearance without secondary sex characteristics. Measured 134 cm in length and was estimated to weigh 85 lbs. Trunk, head and limbs well proportioned and symmetrical. Skin soft, smooth and elastic with moderate amount of subcutaneous fat. Teeth in good condition. No skeletal deformity. Testicles undescended, no pubic hair. Redundant prepuce. Brain weighed 1450 grams, slight edema, vessels normal. The pituitary gland only half filled the sella turcica. It was small, rounded, weighed 0.20 gram and showed no evidence of tumor. The anterior and posterior lobes were of normal proportions to each other. The accessory nasal sinuses were free of infection. The mucosa of the trachea, larynx and epiglottis was reddened, edematous, irregularly eroded and covered with a pseudomembranous deposit. The thyroid was small, weighing only 10 grams but was normal in appearance. The thymus was of normal appearance and weighed 14 grams. The lungs showed an early bronchopneumonia at both bases. The heart appeared normal, showing no hypertrophy. The aorta, radials and femoral arteries showed no abnormality. There was a slight amount of clear fluid in the peritoneal cavity. Spleen, liver and gastrointestinal tract were normal. Adrenals large, weighing 8.75 grams each, but of normal appearance. The testes were in the inguinal canals, small, soft, each the size of a lima bean, weighing together 4.5 grams.

Genito-Urinary Tract The kidneys were slightly larger than usual, flabby and embedded in a considerable amount of fat. The right measured 11 by 6 by 2.8 cm., and the left 10.2 by 5 by 2.8 cm. The capsules were adherent, the surfaces, nodular and cystic. On the cut surface the kidney tissue, largely replaced by large, cyst-like dilatations of the calyces containing a cloudy fluid, appeared as a tough white shell. The cortex and medulla could not be differentiated. There were no abscesses or streaky suppuration as seen in acute pyelonephritis. The pelves were large dilated sacs, and both ureters were widely dilated, measuring up to 3.5 cm. in circumference. There was no obstruction in the ureters and each could be readily traced into the bladder. The bladder wall was greatly hypertrophied, trabeculated. The mucosa was pale, smooth with occasional areas of congestion.

No obstruction was found in the prostatic urethra, although the urethra was transected after examination from the bladder end. The penis was removed and the urethra opened carefully but no point of obstruction could be found.

Microscopically the kidney showed great reduction in the number of glomeruli, those in the outer cortical zone being completely fibrosed, while in the deeper portions those remaining showed marked variation in size with pronounced thickening of the capsular membrane. There was marked separation and extensive loss of tubules due to a great increase of fibrous tissue. Some of the remaining tubules contained hyaline casts. In several areas there were focal collections of lymphocytes and polymorphonuclear leukocytes, and in addition lymphocytes were scattered diffusely throughout the interstitial tissue. The blood vessels were not markedly thickened.

The pituitary gland showed a symmetrical atrophy, the relative proportions of anterior to posterior lobe being essentially the same as in the normal hypophysis. In the anterior lobe, the acidophilic cells were abundant but not evenly distributed, there being a definite tendency to clumping without any specific relation to blood sinuses. The chromophobes were increased in number, being equal to if not greater than, the number of acidophile cells. There were relatively few basophiles distributed about the peripheral portions of the lobe, but they were more abundant in the region of the stalk.

Search of the thyroid and adjacent tissues revealed one large parathyroid gland measuring 4 by 2 mm. Microscopically the cells were all of one type, the large clear chief cells. No acidophilic (oxyphil) cells were seen. A few scattered collections of fat cells were present.

The testis showed a definite increase in the number of interstitial cells. The seminiferous tubules, however, were juvenile in type, the lining cells being limited for the most part, to a single layer of epithelial cells, the spermatogonia and Sertoli cells. In some instances spermatocytes of the secondary layer could be made out, but no further stage of spermatogenesis was evident.

A section of the spinal column at the level of the first lumbar vertebra showed between the cartilaginous plate and the cancellous bone an irregular line of endochondral osteogenesis. The normal arrangement of the cartilage cells in columns was partially destroyed. The bony trabeculae were irregular and thicker than normal, showing water marking to quite a marked degree, each containing a central core of irregular moth-eaten bluish staining matrix and an outer smooth layer involved in patchy areas by small buds of cellular connective tissue containing osteoclasts. The marrow appeared normal.

Microscopically all the other organs were without any significant pathological change.

DISCUSSION

Of the many interesting pathological features of this case one of the most striking was the occurrence of an unexplained dilatation of the urinary tract.

Undoubtedly some obstructing factor or mechanism was present, and its apparent site was obviously at the bladder neck or below this level, as the bladder was uniformly hypertrophied. Unfortunately, in our case the entire urinary tract, including the urethra, was not removed in continuity, the urethra being severed just below the prostate. Consequently, though careful examination of the prostatic urethra, and subsequently the penile urethra, failed to establish any cause for the obstruction, the possibility, as pointed out by Poynton and Sheldon,⁶ that the method of removal destroyed the evidence, such as a valve or incomplete septum at the site of transection, is naturally to be considered. These authors believe that most of these cases are the result of definite organic obstruction rather than a functional disorder of the neuro-muscular mechanism controlling the urethro-vesical sphincter, as suggested by Ellis and Evans.

That clinical evidence of such an obstruction in the posterior urethra may be entirely lacking, was shown by Hinman and Kutzman⁷ who collected 50 reported cases of congenital valvular obstruction of the posterior urethra. They found that frequently the characteristic symptoms such as dribbling, incontinence, and dysuria did not become obvious until infection of the dilated urinary tract occurred. This was borne out by the case of Ellis, but in our case, though infection was undoubtedly present, at no time were symptoms of obstruction present, even as a terminal event.

The suggestion that infection may be the primary factor was mentioned by Mitchell⁸ as a possible explanation of these cases of dilatation without any organic lesion. Obviously this is in contrast to the usual sequence of events, and the origin of the infection remains therefore to be explained.

The many other cited causes which might lead to obstruction, such as congenital torsion of the penis, phimosis, atresia of the urethra, congenital hypertrophy of the vera montanum, cysts of the urethral mucosa and prostate were not operative in this case. Mitchell quotes Sawyer as having had two cases in which he attributed the obstruction to a long prepuce. In our case there was a redundant prepuce, but such a cause is untenable, in view of the fact that many such conditions are present in infancy and unless complicated by some other factor, such as phimosis, do not lead to obstruction.

The kidney findings in this case suggest the changes of both chronic interstitial nephritis and ascending infection. It is obviously difficult, however, to determine what part in the production of these lesions was played by each of these two conditions, nor is it possible to say which was the primary factor.

Due to the insidious onset and long protracted course of the disease, these children do not, as a rule, come under observation until either lack of development or bone deformities become evident. The early history of thirst and polyuria provides interesting data for speculation. There is some evidence according to Mitchell that congenital nephritis may occur, and Ellis suggests that both the dilatation and nephritis may have that origin. He further points out that if the chronic nephritis is a result of back pressure in previously normal kidneys, the type of obstruction which would produce such a result would appear to be one of slight degree.

The solution of the entire problem lies in a much earlier and closer examination of these children before the advanced changes in the urinary tract so obscure the picture that the true etiological basis cannot be determined.

The dwarfism occurring in these cases has been almost universally attributed to an altered metabolism as a result of the long standing renal insufficiency. Its mode of production has never been explained. Throughout the literature, little or no reference has been made to the pituitary gland, beyond the statement that in some instances it was either normal or smaller than normal. The first clear suggestion came from Hutinel⁹ who described a typical case of renal rickets which at postmortem did not show any interstitial nephritis and he regarded the dystrophy as due to an alteration of the glands of internal secretion, particularly the hypophysis.

In Ellis and Evans' series, the pituitary was mentioned only in case 7, in which a cyst was found on the superficial aspect of the pars intermedia. R. W. B. Ellis stated in his case that the appearance of the pituitary was within normal limits. A roentgenogram on the skull of a case reported by Zundell¹⁰ showed a normal pituitary fossa. Feiling and Holyoak¹¹ noted that in their case, though no definite abnormality could be seen, the sella turcica was small and ill-developed.

In those cases of dwarfism where the pituitary is primarily at fault, the anterior lobe deficiency is inherited and in most cases there is a definite family history. Moreover the cases are recognized early. On the other hand, the dwarfism occurring in these renal cases is not apparent for some time. Usually they are normal at birth and continue so until about the seventh year after which time the retardation in growth slowly becomes evident.

In the light of our present knowledge, interpretation of the findings in the pituitary, though suggestive, are inadequate and naturally open to much criticism. They are, however, extremely interesting, and for that reason merit consideration.

If, as Bell¹² points out, the cellular constituents of the anterior lobe represent different stages in the activity of a single cell type, namely the acidophilic cells indicating the secretory phase, the basophilic a storage phase and the chromophobes the resting or exhaustion phase, the predominance here of the chromophobic cells might be interpreted as indicative of an exhaustion phase in the gland. What, if any significance can be attached to the peculiar clumping of the acidophilic cells is impossible at present to say. Their numbers showed no definite increase or decrease.

Rasmussen¹³ has shown in numerical counts on normal glands that the chromophobes may constitute as high as 57 per cent of the anterior lobe cells, with an average of approximately 52 per cent, and a comparatively wide range of variation. Also that the chromophile series may show considerable variation, though not to so marked a degree. In view of these normal variations any approach from the numerical angle, in disease states, must be made with caution before assigning to the results any pathological significance.

These observations were made, however, on normal adult glands, and it does not follow that equivalent conditions obtain in the actively growing period of the first decade.

The suggestion is made that this exhausted and atrophied gland may be the result of a secondary effect exerted upon it by some single or complex product arising as a result of the slowly increasing metabolic disturbance, consequent on the renal disease. A point is reached when there is a relative anterior lobe insufficiency, that is, the demand exceeds the supply, and consequently there is a slow but progressive retardation of somatic, genital and osseous growth.

The bone changes in these cases are interesting, particularly as regards their frequency, mode of origin, and the question whether they are identical with those described in true infantile rickets.

The high incidence and sudden onset of the bone deformities have been well described by Barber,¹¹ Parsons,¹² Lathrop,¹⁰ and Mitchell. The average age at which they develop would seem to be about the ninth year, and their importance is reflected in the fact that their presence may be the first evidence of the true underlying condition. Of these deformities, genu valgum is the most frequent and most important. Barber further points out that the deformities are uncommon in the first few years of life, and in many instances have only appeared at puberty. In the case described by Ellis the typical deformity occurred relatively early, at four years and 10 months, while in our case there was no clinical evidence of any bone deformity, and it was not until examination of a section taken from the vertebral column at postmortem, that definite bone changes were found. Unfortunately, important clinical data such as serum calcium and phosphorus estimations and radiological studies of the long bones were not obtained, attention being particularly directed toward the treatment of the acute uremic state.

Most of the discussion and speculation directed toward an understanding of the fundamental problems in the so-called cases of renal rickets have to do with the chemical changes in the blood, with particular emphasis laid on the relative concentrations of the inorganic phosphorus and calcium.

The usual finding has been a raised serum phosphorus due to the extreme functional disability of the kidney to excrete phosphate, and a lowered serum calcium consequent on the hyperphosphatemia (Peters and Van Slyke¹⁷). Based on this altered ratio, Lathrop, and Shepley, Park, McCollum and Simmonds¹⁸ have suggested that renal dwarfism is a type of low calcium rickets which results from the effects of high serum phosphorus on serum calcium and calcification. The studies of Boyd, Courtney and MacLachlan,¹⁹ Schoenthal²⁰ and Parsons support this view. On the other hand, Hunter²¹ states that "The theory that phosphate retention, due to the renal defect is primarily responsible for the changes in the bones is clearly unsatisfactory." He further points out that in rickets there is a disturbance of exogenous metabolism resulting in a deficient calcification of osteoid tissue, because of a lack of proper metabolism of calcium and phosphorus in the absence of vitamin D, whereas, in renal rickets, though the bone changes may be identical with true rickets, here vitamin D is not lacking and the changes in bones are due to a disturbance of endogenous metabolism of calcium and phosphorus, for which the renal insufficiency, as a result of the chronic nephritis or its equivalent chronic renal obstruction, is responsible.

Two very interesting studies dealing with parathyroid involvement in these cases were made by Smyth and Goldman²² and Langmead and Ori.²³ The former authors, reporting a case of renal rickets, parathyroid dysfunction and metastatic calcification in a boy of 14 years, the underlying cause of which was a congenital urethral obstruction, found that the retention of acid phosphate constituted the first important change in the blood chemistry and, while agreeing with the theory based on the high level of blood phosphorus, suggest that the raised serum phosphorus stimulates the parathyroid glands (parathyroid hyperplasia) resulting in dwarfism and demineralization of the bones. Langmead

and Ori suggest as an explanation of the bone changes that although the chronic renal disease occurring in renal dwarfism may cause true rachitic changes in bones the most characteristic osseous changes seen radiographically are due to osteoclastic resorption, the result of secondary parathyroid activity

Mitchell, from his extensive review of the literature concluded that clinically the bone changes were identical with those seen in the usual infantile rickets but that radiologically and histologically they appear somewhat different With regard to the latter, Brockman's study of the histological changes would seem to indicate that although both show the irregular line of ossification with formation of irregular bony trabeculae, destruction of cartilage cells increased number of blood capillaries, and replacement of red marrow in relation to the trabeculae, with fibrous tissue, in renal rickets these changes are much more marked, with slight differences sufficiently evident to distinguish between them

In our case we feel, therefore, that the changes described do not warrant any definite conclusion as to the possibility of their being rachitic in type but that they merely indicate a general inhibition of growth

SUMMARY

- 1 A case of renal dwarfism is reported
- 2 The interesting finding of a marked dilatation of the urinary tract and hypertrophy of the bladder, unsuspected clinically, is discussed
- 3 The urinary retention appeared to occur at the level of the urethro-vesical sphincter No obvious organic cause for the obstruction was found
- 4 Of particular interest were the marked changes in the pituitary gland, and the hypothesis is suggested that the dwarfism may be due to a secondary effect on the pituitary of some product of altered metabolism arising as a result of the long standing renal insufficiency
- 5 Definite microscopic changes in the bone of the vertebral column are described and are interpreted as evidence of a general inhibition of growth

REFERENCES

- 1 FLETCHER, H M Case of infantilism with polyuria and chronic renal disease, *Proc Roy Soc Med (Sect Dis Child)*, 1911, iv, 95
- 2 LUCAS, C A form of late rickets associated with albuminuria, *Lancet*, 1883, i, 993
- 3 BARBER, H Renal dwarfism, *Quart Jr Med*, 1920, xiv, 205
- 4 ELLIS, A and EVANS, H Renal dwarfism *Quart Jr Med*, 1933, 231
- 5 ELLIS, R W B Renal dwarfism, *Lancet*, 1935, i, 142
- 6 POYNTON, F J, and SHELDON, W P H On dilatation of the bladder and ureters in childhood, *Arch Dis Child*, 1927, ii, 251
- 7 HINMAN, F, and KUTZMAN, A A Congenital valvular obstruction of the posterior urethra, *Jr Urol* 1925, xiv, 71
- 8 MITCHELL, A G Nephrosclerosis (chronic interstitial nephritis) in childhood, *Am Jr Dis Child*, 1930, xli, 101, 343
- 9 HUTINEL, V *Abstr in Brit Jr Child Dis*, 1912, ix, 513
- 10 ZUNDEL, C E Two cases of infantilism, *Proc Roy Soc Med (Sect Dis Child)*, 1913, vii, 1
- 11 FELLING, A and HOLLOAK, W L Case of renal dwarfism with optic atrophy, *Proc Roy Soc Med (Chn Sect)*, 1921, xvi, 1
- 12 BELL, B The pituitary, 1919, Bailliere, Tindall and Cox, London

- 13 RASMUSSEN, A T The percentage of the different types of cells in the male adult human hypophysis, *Am Jr Path*, 1929, v, 263
- 14 BARBER, H The bone deformities of renal dwarfism, *Lancet*, 1920, i, 18 Renal dwarfism, *Guy's Hosp Rep*, 1922, lxxii, 62 Renal dwarfism, *Guy's Hosp Rep*, 1926, lxxvi, 307
- 15 PARSONS, L G The bone changes occurring in renal and coeliac infantilism, and their relationship to rickets, *Arch Dis Child*, 1927, ii, 1, 198
- 16 LATHROP, F W Renal dwarfism, *Arch Int Med*, 1926, lxxviii, 612
- 17 PETERS, J P, and VAN SLYKE, D D Quantitative chemical chemistry, 1931, Williams and Wilkins Co, Baltimore
- 18 SHEPFLY, P G, PARK, E A, McCOLLUM, E V, and SIMMONDS, N Is there more than one kind of rickets? *Am Jr Dis Child*, 1922, lxxiii, 91
- 19 BOYD, G L, COURTNEY, A M, and MACLACHLAN, I F The metabolism of salts in nephritis, *Am Jr Dis Child*, 1926, lxxii, 29
- 20 SCHOENTHAU, L, and BURPF, C Renal rickets, *Am Jr Dis Child*, 1930, lxxix, 517
- 21 HUNTER, D Critical review the metabolism of calcium and phosphorus and the parathyroids in health and disease, *Quart Jr Med*, 1931, lxxiv, 393
- 22 SMYTH, F S, and GOLDMAN, L Renal rickets with metastatic calcification and parathyroid dysfunction, *Am Jr Dis Child*, 1934, lxxviii, 596
- 23 LANGMEAD, F S, and ORR, J W Renal rickets associated with parathyroid hyperplasia, *Arch Dis Child*, 1933, viii, 265

ACUTE FULMINATING MENINGOCOCCUS INFECTION WITH BILATERAL CAPILLARY HEMORRHAGE OF THE ADRENALS AS THE MOST STRIKING GROSS PATHOLOGIC LESION, A CASE REPORT¹

By F H FOUCAR, F A C P, Lt Col, Medical Corps, U S Army

THE case I shall report died 12 hours after the onset of the final illness, one-half hour after admission to the Walter Reed General Hospital. The antemortem diagnosis was Rocky Mountain spotted fever. As no antemortem laboratory work of any kind had been done and as only a very superficial physical examination had been possible, the microscopical studies on the autopsy material were undertaken to substantiate or refute the original diagnosis. The final diagnosis was not made until after a careful microscopical examination of the body tissues had been completed. The author deems the case especially valuable as an illustration of the solution of a problem in postmortem diagnosis.

CASE REPORT

W H, a white male, aged 20 years. A member of the Civilian Conservation Corps, attached to Camp A2, Beltsville, Md. He always had been in good health and exceptionally strong and active. He worked Saturday, Sept 21, 1935, until noon when he was given a pass for the weekend. According to the statement of the patient's brother the patient was perfectly well until Sunday evening. Sunday evening, September 22, the patient "suddenly came down with chills and fever, and brown spots appeared over his body, he complained of pain in his joints." The family physician was called who made the diagnosis of Rocky Mountain spotted

¹ Received for publication December 2, 1935

From the Laboratory Service, Walter Reed General Hospital, Washington, D C

fever Monday morning, September 23, the patient's brother transported him in an automobile from Landsdowne, Md, to Camp A2, arriving at the Camp Dispensary at 8 30 a m At this time the patient presented the picture of a hemorrhagic purpura involving practically the entire body He was conscious, answered questions intelligently and did not appear to be in great pain He was immediately transferred to the Walter Reed General Hospital, Washington, D C

The patient was admitted to the Walter Reed General Hospital, Monday, September 23, at 9 45 a m He presented what was described by the Ward Surgeon as a hemorrhagic discoloration of the skin over the entire body Conjunctivae hemorrhagic Pupils equal in mid-dilatation Lips cyanosed Pulse almost imperceptible The heart sounds were distant and the blood pressure too low to determine The patient became comatose within 15 minutes after admission He vomited about 250 c c of "greenish mucus" He died at 10 15 a m, one-half hour after admission to hospital

Autopsy, W R G H Autopsied September 23, 1935 at 10 45 a m, 30 minutes after death The following is an abstract of the protocol

Body that of young adult white male, length 174 cm, weight 77 kg Well nourished, voluntary musculature exceptionally well developed Right pupil 6 mm in diameter, left 5 mm No exophthalmos There is marked subconjunctival hemorrhage, bilateral The left deltoid region presents two large vaccination scars The cutaneous surface of the body shows a diffuse erythema, ham colored, most advanced over face, neck, arms and extensor surfaces of forearms Ears cyanosed The thighs and legs are only slightly "flushed" The palmar surfaces of the hands and feet are of normal hue After removal of the viscera and consequent drainage of blood, the cutaneous erythema paled considerably leaving scattered bluish petechial areas over the forehead and surrounding the mouth

Thymus rest 25 gm Thyroid 25 gm Congested

Lungs Right 450, left 400 gm Upon the pleural surface of all lobes both lungs are scattered small bright red points of hemorrhage, 1 to 2 mm in diameter *Heart* 370 gm The epicardial surface presents scattered points of hemorrhage The wall of the left ventricle is 1.9 to 1.4 cm in thickness, cut surfaces grayish-red, consistence firm The aortic ring is 6.5 cm in circumference The valves are normal The heart contains fluid blood The coronaries are normal Aorta intima smooth, glistening and of a normal ivory hue

Abdomen There are widely scattered, small points of hemorrhage over the stomach, jejunum and ileum and over both leaves of the mesentery of the small gut There is no increase in fluid in the peritoneal clunk Stomach Slightly dilated Mucosa grayish-red, rugae preserved No eschars, no ulcers The lumen of the stomach contains 250 c c of grass green fluid without appreciable odor Jejunum Wall slightly edematous, mucosa pink, glistening and shows normal markings The mucosa presents a few petechial hemorrhages, 2 to 4 mm in diameter The lumen contains a small amount of semi-solid pale yellow material Ileum Contracted, contents scant in amount and of pale yellow hue The mucosa of the lower ileum presents six to eight oval areas measuring from 1 to 3 cm in length, long axes paralleling the long axis of the bowel The oval areas are grayish, finely granular and lusterless, edges sharp Vermiform appendix Normal in the gross Colon The ascending, transverse and descending colon are contracted, mucosa pale, moist and glistening There are a few scattered petechial hemorrhages, 2 to 4 mm in diameter, bright red in color, located in the mucosa The rectum and sigmoid contain fluid feces, no gross blood The mucosa lining the rectum is pale gray and presents scattered petechiae and innumerable pin-point hemorrhages The lymph nodes in the mesentery of the small gut are enlarged to the size of split peas, pinkish-gray and shotty to the feel Liver 1630 gm No gross pathology Spleen 160 gm Consistence firm Cut sur-

faces flat, glistening and of a deep plum color. Corpuscles not visible in the gross. Pancreas 110 gm. Normal in the gross.

Adrenals The adrenals furnish a striking gross appearance. The combined weight of the two adrenals is 25 gm (normal 12 to 15 gm). They are of normal contour, firm and of a dark slate color. The cut surfaces show marked capillary hemorrhage throughout the cortices and invading the medullary portions. The cut surfaces of the adrenals are flat and of a reddish brown hue. Small islands of grayish translucent medullary parenchyma are visible. Both adrenals present the same gross picture (Figures 1 and 2).

Kidneys Right 170, left 180 gm. Cut surfaces show moderate congestion. Urinary bladder, prostate, seminal vesicles, vasa deferentia and testes. Normal in the gross.

Calvarium Normal. **Dura** Moderate edema. **Brain** 1370 gm. Consistence quite soft. The pia is congested. The ependyma is smooth and glistening. There is marked congestion of the small vessels beneath the ependyma covering the floor of the fourth ventricle. **Pituitary** Normal. The circle of Willis and cerebral arteries present normal walls and contain fluid blood.

The outstanding gross findings are (1) cutaneous erythema with purpuric areas, (2) scattered points of capillary hemorrhage upon the serous surfaces of the viscera, (3) hyperplastic Peyer's patches and enlarged mesenteric lymph nodes, (4) bilateral capillary adrenal hemorrhage, (5) congestion of the pia arachnoid.

Considering the above gross findings singly the diagnoses suggested are Rocky Mountain spotted fever, typhoid fever, bilateral capillary hemorrhage of the adrenal, possibly toxic as in diphtheria, possibly septic, bulbar palsy. The final diagnosis was not made until the above possibilities were eliminated.

As suggested by the gross pathological findings, the following bacteriological examinations were made:

(a) Cultures from the nares and the nasopharynx upon Loeffler's medium were negative for the diphtheria bacillus.

(b) Culture from the heart's blood was overgrown by *B. coli*.

(c) Culture from spleen showed no growth.

(d) Cultures from the contents of the lower ileum, caput coli and from the surfaces of the Peyer's patches all were negative for bacilli of the typhoid-dysentery groups.

Blood serum of the deceased was agglutinated against *B. proteus* X-2, proteus X-19 and proteus Kingsbury, all agglutinations were negative.

Blood taken from a subcutaneous venule of the cadaver shows the following differential count: lymphocytes 38, monocytes 17, neutrophils 45 per cent. The lymphocytes are all of the small type. The neutrophils are 28 per cent band forms and 17 per cent segmented forms. The granulocytes present advanced degenerative changes. Gram stain of blood film shows no microorganisms.

Microscopical examinations were made of all the organs of the body, stained both by H. E. and Giemsa. Especial attention was paid to the reaction of the blood vessels of the skin, brain and heart in view of the original diagnosis of Rocky Mountain spotted fever^{1,2}. There is no endothelial swelling or hyperplasia and no thrombosis. The perivascular reaction is limited to the skin where there is engorgement of the venules in the zone between the corium and hypodermis, the congested subpapillary venules present an irregular piling up of the adventitial cells including a considerable number of mast cells and an occasional lymphocyte. The capillaries supplying the sweat glands and the papillae of the hair follicles show no pathologic changes. None of the histiocytes or endothelial cells include Rickettsia. There are no perivascular nodules in the heart, and sections of the testes show normal histology. The histopathology of Rocky Mountain spotted fever was fresh in my mind due to a case autopsied recently. Dr. R. D. Lillie of the National Institute of Health kindly studied



FIG 1 *Adrenals* combined weight 25 gm Dark slate color in the gross



FIG 2 *Adrenal* cut surfaces frt, reddish-brown, markings greatly obscured

the slides I made in the case I am now reporting and found nothing suggestive of Rocky Mountain spotted fever

The micro-sections of the lower ileum show hyperplasia of the Peyer's patches, the germinal centers are prominent and present small areas of karyorrhexis and beginning necrosis (figure 3) No bacteria are revealed by the Giemsa stain The

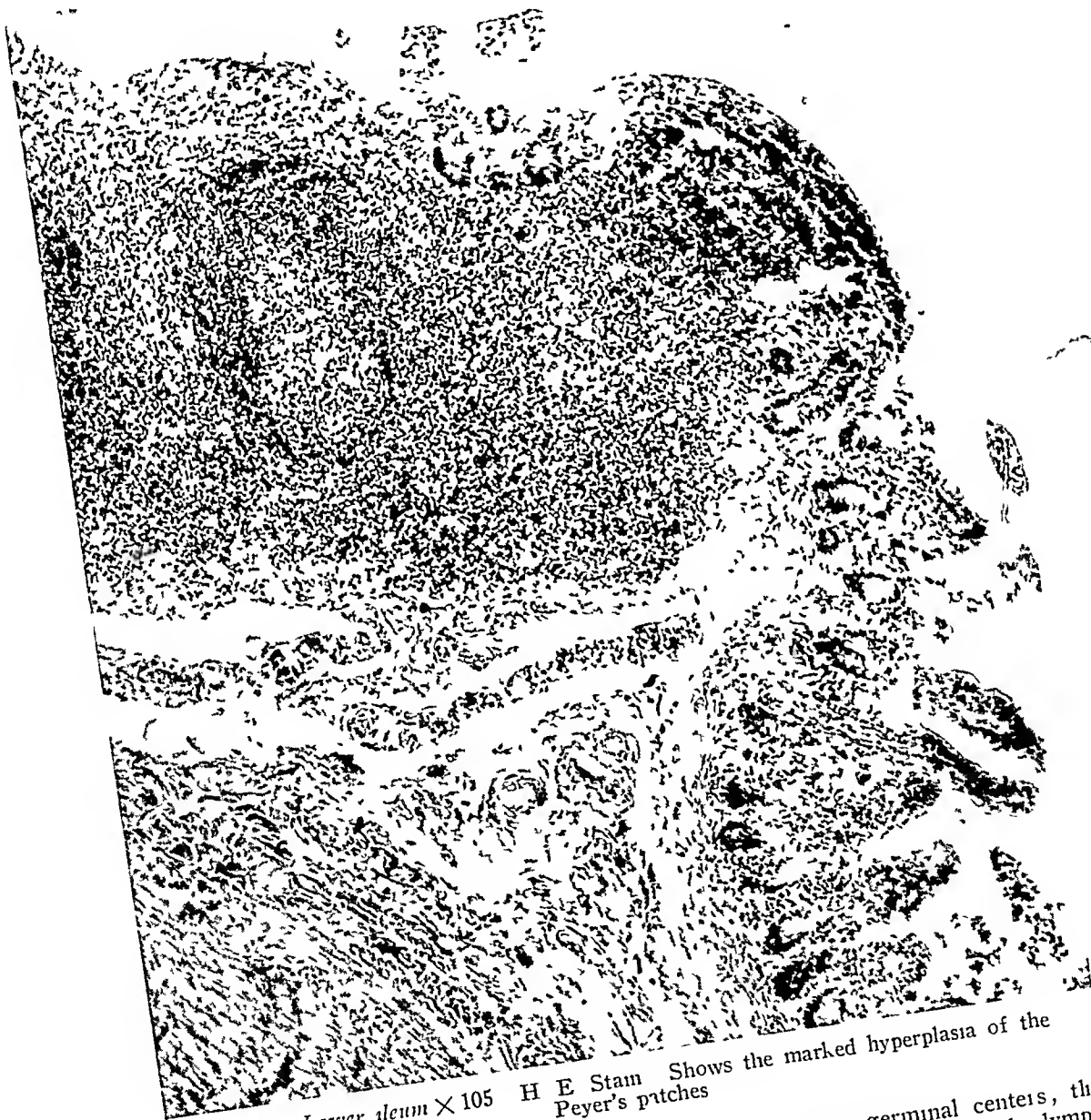


FIG 3 Lower ileum $\times 105$ H E Stain Shows the marked hyperplasia of the Peyer's patches

lymph nodules in the mesentery of the ileum present large germinal centers, the sinusoids do not show the large swollen phagocytic reticular cells found in the lymph nodes in cases of Rocky Mountain spotted fever

Adrenals The surrounding fat presents a diffuse, very slightly marked infiltration with erythrocytes. The arteries show normal walls, the veins are congested. The adrenal capsule is thin and intact. The zona glomerulosa is fairly well represented. Beneath the capsule there is marked capillary hemorrhage extending inward in broad rays and wedge-shaped areas. The remnants of cortex are well preserved, the cells rich in lipoids. The zona reticularis is entirely replaced by hemorrhage (Figure 4). The medullary portion is for the most part destroyed by hemorrhage though there are scattered islands of parenchyma remaining. The intact portions of the medulla show capillary congestion, edema, and small agminations of lymphocytes and plasma cells. Sections stained by Giemsa and by Gram reveal no microorganisms. Sections stained by Levaditi show no treponemata.

The microscopic examination of thyroid tissue reveals large acini filled with deeply stained, homogeneous colloid, epithelium flattened. No apical vacuoles. No lymphoid reaction.

The parathyroid section includes a lobule composed of high cylindrical clear cells. The majority of the lobules present alveoli composed of small clear cells, the large polygonal oxyphilic cells are very few in number.

Pituitary No pathologic changes other than venous capillary congestion.

Brain Sections were taken from the medulla at the level of the decussation of the pyramids and at the level of the inferior olive and sensory decussation, also from the cortex of the forebrain (left precentral gyrus), the basal ganglion left, including the internal capsule, caudate nucleus and ependyma lining the lateral ventricle. The sections were stained by H. E. and by Giemsa. The microscopic picture shows congestion of the veins and capillaries in the arachnoid, edema of the molecular layer which includes swollen astrocytes. There is capillary congestion throughout the gray substance and a few small hemorrhages into the perivascular spaces of His. No ring shaped hemorrhages. No thrombosis. No cellular infiltration of the spaces of Virchow-Robin and no perivascular cellular "cuffing."

Sections of the brain stained by Gram show many small Gram-negative diplococci arranged in small groups and in scattered pairs, mostly extracellular though a few of the diplococci are included in the bodies of adventitial cells. The Gram negative diplococci are coffee bean shaped, without capsules and are found in the cellules of the arachnoid over the ventral surface of the medulla and over the outer surface of the forebrain (Figure 5).

Gram stain made of the sections of the skin and adrenal reveal no bacteria.

Diagnoses Acute fulminating meningococcus infection with general purpura and massive bilateral capillary adrenal hemorrhage. *Death* occurred before the onset of a suppurative meningeal reaction.

The bilateral adrenal hemorrhage is very striking, and at one period in the study of the case I was tempted to call the adrenal hemorrhage the cause of death without searching further for a cause of the general pathologic process. The histogenesis³ of the adrenals and the dual function^{4,5} of these organs should be reviewed by those who are interested in the adrenal lesions encountered in the case I have just presented. The subject of bilateral adrenal hemorrhage had been brought to my attention by Lavenson⁶ and by Pearl and Brunn.⁷ The adrenal hemorrhage in the cases cited by these authors is of the thrombotic type, secondary to a local inflammatory reaction in the case of Lavenson, possibly syphilitic in the case cited by Pearl and Brunn. The bilateral adrenal hemorrhage in the case I have reported in this paper is of the capillary type, suggesting a toxemia as in diphtheria or a fulminating septicemia. The case of Rocky Mountain spotted fever recently autopsied at this hospital presented unilateral adrenal hemorrhage of the thrombotic type. Whether or not the adrenal damage

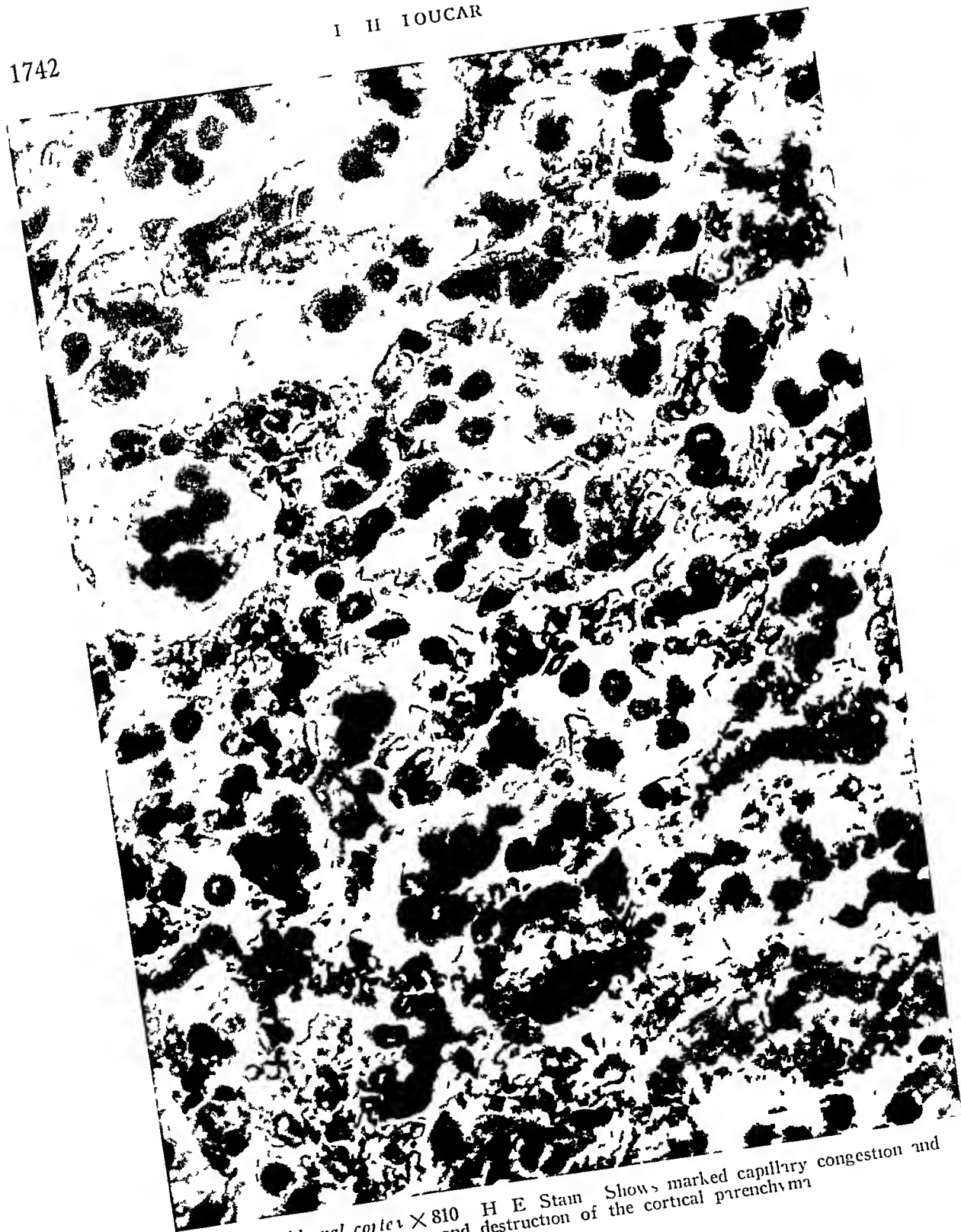


FIG 4 *Adrenal cortex* $\times 810$ H E Stain Shows marked capillary congestion and hemorrhage and destruction of the cortical parenchyma

in the case I have just reported had any direct bearing upon the rapidly fatal termination, is problematical. Blasses⁸ (quoted by Peail and Brunn) states that massive bilateral adrenal hemorrhage causes an initial hyperadrenalemia followed by hypoadrenalemia resulting in death.

The original diagnosis of the case I have just presented was Rocky Mountain spotted fever, suggested by the cutaneous eruption and no doubt by the fact that cases of this disease had been recently encountered in this section of the United States. In the course of my microscopical examinations I excluded Rocky Mountain spotted fever as the final diagnosis. The negative Weil-Felix reaction here means nothing because of the very short period of time elapsed since



FIG 5 *Arachnoid*, ventral surface of the medulla oblongata, level of the pyramids $\times 2050$ Gram stain. Shows Gram-negative diplococci in clumps without associated inflammatory reaction other than presence of few lymphocytes and wandering histiocytes.

the onset of the illness. Cecil⁹ quotes Wolbach as follows: "In Rocky Mountain spotted fever the rash appears usually on the third to fifth day of the fever. The rash appears first on the wrists, ankles and back, then on the forehead, arms, legs, chest and abdomen. The efflorescence requires 24 to 36 hours. The macules are at first bright red, rapidly become darker and after a few days the eruption is definitely petechial." In the case just presented the eruption came on within a few hours following the initial chill and was general and purpuric from the start.

A typical case of Rocky Mountain spotted fever is presented by Masson¹⁰. This case will serve well as a model in both the diagnosis and differential diagnosis between Rocky Mountain spotted fever and other exanthemata, giving as it does the incubation period (5 days), the mode of onset, the appearance and

distribution of the eruption and the dates and titers of agglutinations of the patient's blood serum against proteus X-19. In Masson's case of Rocky Mountain spotted fever the eruption first appeared upon the wrists and ankles during the third day of the illness and was of the red macular type, on the fourth day of the illness the "rash" became generalized, involving the face, trunk and extremities including the palms and soles.

As all of us had overlooked meningococcus infection as a possible etiologic factor in the case I have presented, I shall quote several of the accepted texts on the subject of epidemic meningitis.

Osler's¹¹ definition of cerebrospinal fever is "an infectious disease occurring sporadically and in epidemics, caused by the meningococcus, characterized by inflammation of the cerebrospinal meninges and a clinical course of great irregularity. The affection is also designated as spotted fever. Meningococci may be in the blood without meningitis resulting. In malignant cases there may be no characteristic pathological changes, the brain and cord showing only extreme congestion. The intestine sometimes shows swelling of the follicles." According to Nelson¹² "In fulminating cases the skin, serous membranes and particularly the adrenals show hemorrhages and microscopically the cutaneous blood vessels have been seen to be crowded with meningococci. The Peyer's patches and the mesenteric lymph glands are commonly swollen and the intestinal mucosa may be hemorrhagic. Petechial hemorrhages may be seen on all serous surfaces."

Referring to the notes I made during May 1919, while I was in charge of Army Laboratory No. 1, Neufchateau, France, I find that many cases of meningitis were hospitalized as respiratory diseases, and the final diagnosis of meningitis was made when the patients had been isolated in the influenza wards of Evacuation and Base Hospitals. French pathologists during the early part of the World War reported cases of meningococcic septicemia without meningeal involvement. During Sept. 1918 a case of bronchopneumonia was admitted to Base Hospital No. 6, the sputum of this case yielded a pure culture of the meningococcus, type IV (Pasteur type B).

Boyd¹³ states "In a case of extremely acute meningococcic septicemia in a child which I studied, the only lesion was an extensive bilateral hemorrhage of the adrenals."

Stevens¹⁴ discusses the fulminating type of cerebrospinal fever which he says is comparable to the malignant forms of other specific infections, not uncommon in some epidemics and occasionally met with sporadically. The patient is suddenly stricken, sometimes without the least warning, and quickly passes into a state of collapse. A severe chill, headache, stupor, soon followed by coma, moderate fever, a feeble pulse and an extreme prostration are the usual symptoms and the usual course. A purpuric eruption is present in some cases. Death is inevitable and may take place within 12 hours. Autopsy reveals hyperemia of the membranes of the brain but no pus.

Dr. A. Magruder MacDonald, the Coroner of Washington, D. C., told me that in the epidemic of cerebrospinal meningitis during the winter and spring of 1934 to 1935, there was a high percentage of fulminating cases with a course of from 12 to 24 hours, autopsies revealed no purulent meningeal reaction in these cases.

A recent report¹⁵ of a case very similar to the one I have just presented has come to my attention. By a happy coincidence the case referred to in this paragraph is from the Navy, while my case was under the Army jurisdiction. The Naval case was admitted to the U S S "Relief" from a battleship, March 9, 1935 and died two and a half hours later. As far as could be determined the patient, a white male, aged 18 years, was sick only five hours prior to his death. The antemortem leukocyte count was 5000 with 71 per cent small lymphocytes. The blood film was loaded with Gram-negative diplococci. The antemortem spinal fluid was entirely negative, cell count three. The antemortem blood culture was positive for the meningococcus (type not specified). The autopsy findings in this case show congestion of the meninges but no purulent exudate, there are petechial hemorrhages in the serosa covering all the viscera. The statement is made that "the adrenals are swollen and appear hemorrhagic."

SUMMARY

The case presented is that of a young adult white male who became ill suddenly during the evening of Sept 22 this year. The onset of the illness was marked by a chill, followed by pain in various joints. By morning a general purpuric erythema had developed. The radial pulse became imperceptible, coma developed and the patient died 10 15 a m, Sept 23. The total illness was of less than 12 hours' duration. Autopsy revealed bilateral adrenal capillary hemorrhage as the most striking gross finding. Micro-sections of the brain stained by Gram showed Gram-negative intra- and extracellular diplococci located in the cellulose of the arachnoid. There was no purulent reaction of the meninges. The final diagnosis, based on the microscopic autopsy findings, is acute fulminating meningococcus infection.

CONCLUSIONS

It is misleading to over-emphasize the importance of any single gross autopsy finding, such as the cutaneous erythema, the petechial hemorrhages in the serosa of the viscera, the bilateral capillary hemorrhage of the adrenals, the hyperplastic Peyer's patches and the congestion of the brain, all of which were well marked gross autopsy findings in the case I have presented. In any case presenting a skin eruption, the character and distribution of the eruption and the time required for complete efflorescence must be taken into consideration. The importance of considering meningococcus infection as a possible cause of death in an illness of less than 12 hours' duration is emphasized.

BIBLIOGRAPHY

- 1 WOLBACH, S B. Etiology and pathology of typhus, Research Commission to Poland, Harvard U Press, Cambridge, Mass.
- 2 LILLIE, R D. Pathology of eastern type of Rocky Mountain spotted fever, U S Treasury Dept., Public Health Report, 1931, vol. 1, 2840-2859.
- 3 MAXIMOW, A A, and BLOOM, W. A text book of histology, 1930, W B Saunders Co., Philadelphia, 704-709.
- 4 ENGBACH, W. Endocrine medicine, 1932, Charles C Thomas, Baltimore, 1, 16-17, 170-172.

- 5 ROWNTREE, L G, GRIM, C H, et al Treatment of Addison's disease with cortical hormone of suprarenal gland, Jr Am Med Assoc, 1931, xcvi, 1446-1453
- 6 LAYFARSON, R S Acute insufficiency of the suprarenals, Arch Int Med, 1908, ii, 62-73
- 7 PLARI, F, and BRUNN, H Suprarenal apoplexy, bilateral, Surg, Gynec and Obst, 1928, xlii, 393-400
- 8 BRASSER, A Beitrag zur Kenntnis der Nebennierenblutung, Klin Wchnschr, 1924, iii, 738 (Quoted by F Pearl and H Brunn)
- 9 CICH, LAFAVITI A text book of medicine, by Am authors, 3rd Ed, 1934, W B Saunders Co, Philadelphia, 365
- 10 MASSON, D M Rocky Mountain spotted fever, report of three cases, Proc Staff Meet Mayo Clinic, 1935, i, 658-659
- 11 OSLER, W The principles and practice of medicine, 1931, D Appleton Co, New York and London, 113-114
- 12 NELSON, S Loose Leaf Medicine, 1930, Thomas Nelson and Sons, New York and London, ii, 51
- 13 BOYD, W The pathology of internal diseases, 1931, Lea and Febiger, Philadelphia, 722-723
- 14 STEVENS, A A The practice of medicine, 2nd Ed, 1926, W B Saunders Co, Philadelphia, 90
- 15 BOONL, J T, and HALL, W M Meningococcal septicemia with a report showing organisms in the direct blood smear, U S Naval Med Bull 1935, xxxiii, No 4

LIPOIDAL HISTIOCYTOMA (FIBROXANTHOMA), REPORT OF A CASE

By GEORGE M LEWIS, M D, *New York, N Y*, and WILBERT SACHS, M D, *Jersey City, N J*

THE origin and nature of the xanthoma cell is in doubt¹ Because of this, its significance is not fully understood Many observers have noted the rather widespread occurrence of xanthoma-like cells in dermatoses not usually considered among the true xanthomas In using the term fibroxanthoma, a combination of a fibroma with a xanthoma is implied Aschoff and Kammer² consider that such a unification exists and classify fibroxanthoma as a type of the true xanthomas Pinkus and Pick³ contend that the process is more likely due to the ability of tumors of the connective tissue group to become enriched with lipoids For this reason, they prefer the term fibroma xanthoma or, better still, fibroma lipoidicum We doubt that it is a disease *sui generis* because it apparently has no characteristic clinical features

CASE REPORT

J S, aged 36, a policeman, was first examined in January 1934, regarding a lesion of six months' duration on the right knee Four years before, he was struck by a trolley-car and severely injured Besides several dislocations and internal injuries, he sustained many contusions and abrasions, among which was an abraded area at the site of the present lesion Healing was delayed and a small infiltrated area remained Six months before his first visit, he tripped on a subway stair and

* Received for publication August 21, 1935

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University

bruised the same area of skin on his right knee. Following this, a lesion appeared and became progressively larger until it reached its present size (figure 1). Bleeding was at times profuse, so that it was necessary to wear a bandage to prevent his clothes becoming soiled.

Examination disclosed a walnut-sized, dark-red nodule, elevated above the surface of the skin. Its surface was uneven and in one part was covered with a crust. There was very slight infiltration at the base. Palpation of the lesion revealed a slightly harder consistency than one would expect from its appearance.

From the clinical characteristics, the lesion was considered either sarcoma or pyogenic granuloma. Because of the possibility of malignancy, it was felt advisable

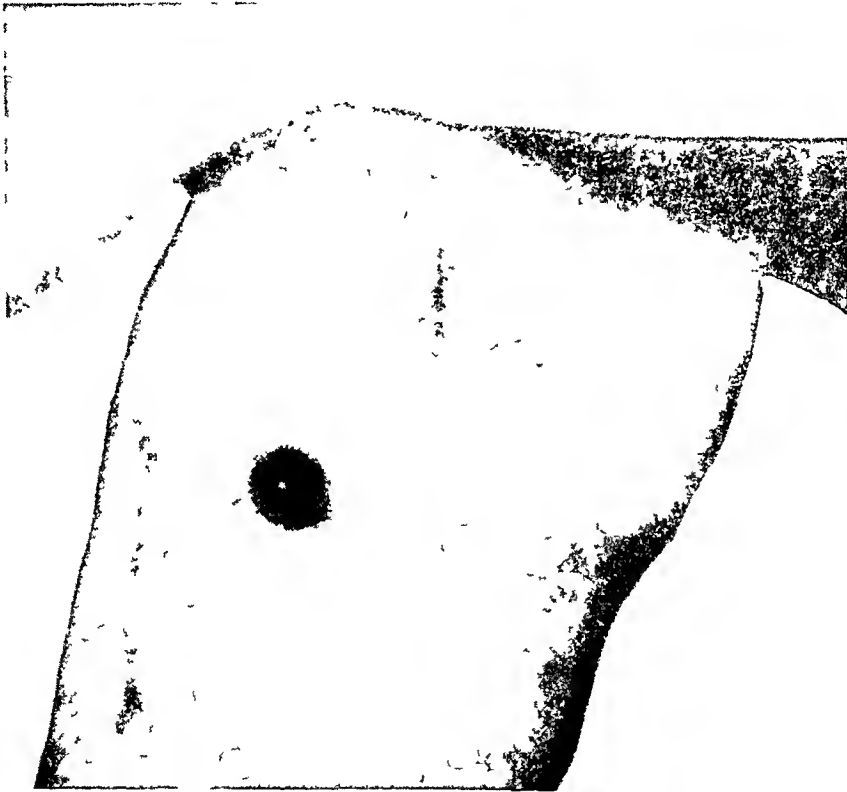


FIG 1 Photograph showing the lesion on the right knee

to excise the lesion. This allowed a complete histologic study to be made. After surgical removal, the wound was closed with three interrupted sutures.

Pathology In the center of the specimen was an infiltrate occupying one-half the section and extending throughout the upper, mid, and deep cutis down to the fat (figure 2). This infiltrate was composed of closely packed cellular elements. The area was circumscribed and sharply differentiated from the normal tissue on either side.

Throughout the infiltrate were coarse and fine strands of connective tissue. Within these were many blood and lymphatic vessels. In the mid and upper cutis these vessels were more numerous and were markedly dilated, some were filled with blood elements.

At the margins of the section, the epidermis was markedly and irregularly acanthotic. The rete pegs encircled the cellular infiltrate and extended down almost

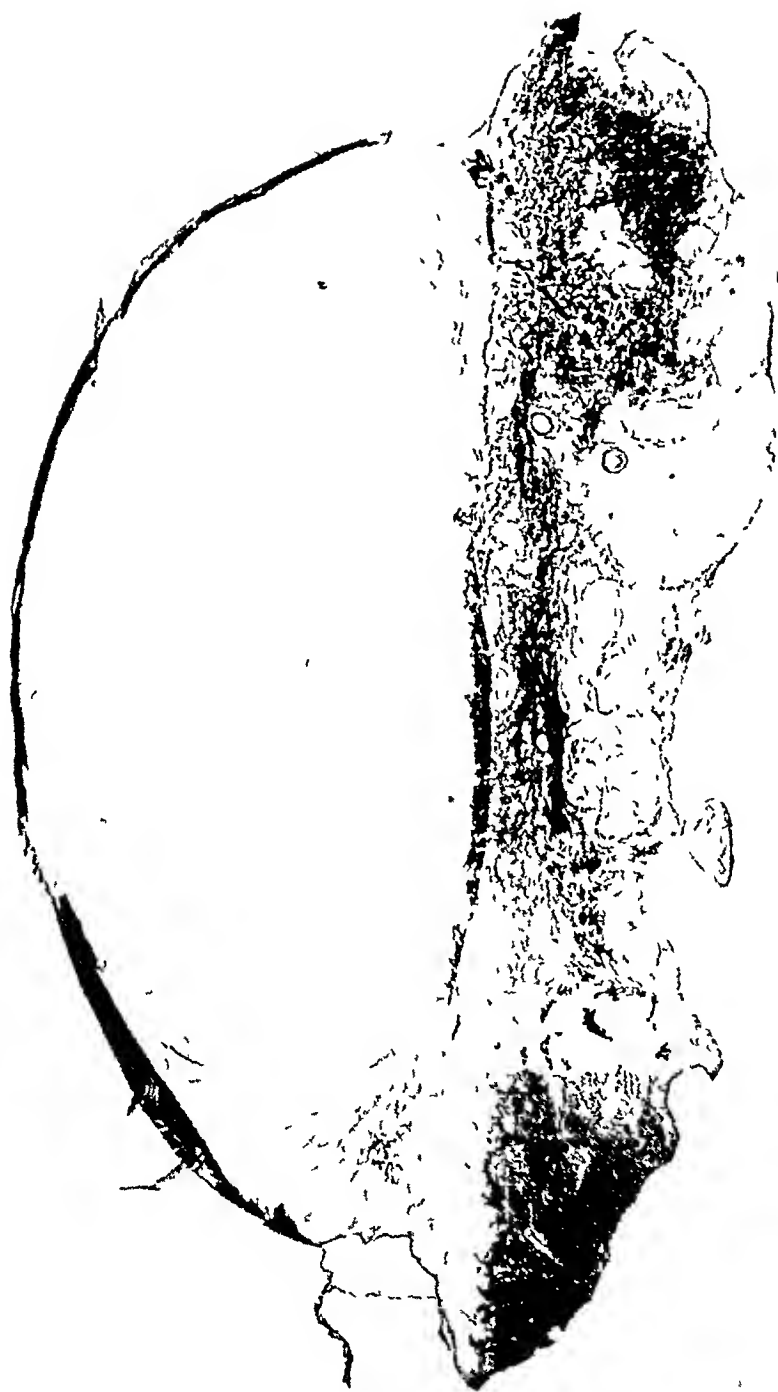


FIG 2 Low power photomicrograph showing the lesion as a whole ($\times 10$)

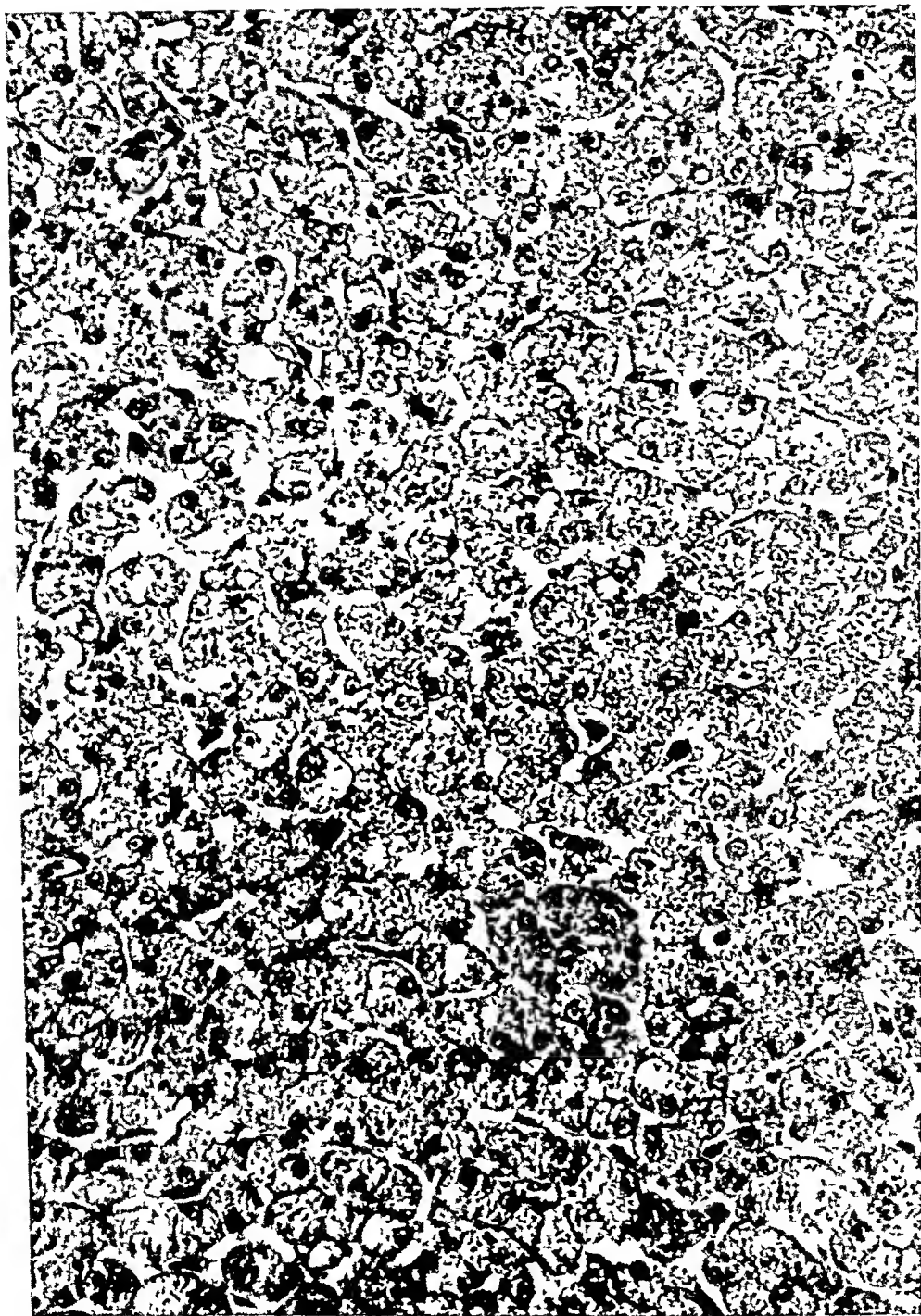


FIG 3 High power photomicrograph showing histiocytes with fatty changes ($\times 500$)

to the deep cutis. Overlying the cellular mass, the epidermis was thinned into a narrow band of three or four layers of cells, composed of one basal cell, one or two prickle cells, and one horn cell. The rete pegs and papillary bodies were absent. Over the center, the epidermis was entirely missing and the cellular mass extended to the surface.

The infiltrate was composed of large cells, some being round and some polygonal, they were about in equal proportion (figure 3). The cell outlines were distinct and the nuclei were large and round, with chromatic fibers loosely arranged. There were definite nucleoli. Many of the cells contained two or three nuclei. The spongiosum was fairly clear but the hyaloplasm was only faintly visible, giving a foamy appearance to the cell body.

Besides the presence of xanthoma-like cells, granuloma pyogenicum was differentiated from fibroxanthoma by the absence of granulation tissue and the presence of a different stroma, sarcoma was ruled out by the absence of variously-sized connective tissue cells, by the fact of the lesion being well circumscribed and demarcated and by its orderly arrangement.

SUMMARY

A case is reported in which the clinical findings were suggestive of either granuloma pyogenicum or of sarcoma. The histology was that of fibroxanthoma. Examination of the patient one year following the removal of the lesion revealed no evidence of local recurrence.

BIBLIOGRAPHY

1. PLEWS, L. W. The nature and origin of the xanthoma cell, *Arch. Path.*, 1934, **vii**, 177.
GRUENTILD, G., and SEELIC, M. G. The nature of so-called xanthoma, *Arch. Path.*, 1934, **vii**, 546.
2. URBACH, E. Lipoid metabolism diseases of the skin, *Handbuch der Haut und Geschlechtskrankheiten*, 1932.

EDITORIALS

THE AMERICAN BOARD OF INTERNAL MEDICINE

During the recent session of the American Medical Association at Kansas City, Missouri, May 11 to 15, 1936, the American Board of Internal Medicine was given final official approval by the Advisory Board for Medical Specialties, the Council on Medical Education and Hospitals and the Section on Practice of Medicine of the American Medical Association.

The Section on Practice of Medicine, American Medical Association, held a special executive meeting for this purpose, preceding the scientific program, Wednesday morning, May 12, 1936 with Dr. William J. Kerr, chairman of the section, presiding. Present on the platform were the four representatives from the Section on the Joint Committee of Organization, Reginald Fitz, Ernest E. Irons, John H. Musser, and Walter L. Biering as well as Dr. James Alexander Miller, recent president of the American College of Physicians.

The plan of organization of the Board with an outline of the methods for certifying specialists in internal medicine was presented by the chairman of the Joint Committee, Walter L. Biering, after which Dr. James Alexander Miller made a statement on behalf of the American College of Physicians that the College appreciated the privilege and opportunity to sponsor this movement and cooperate with the Section in the organization of the American Board of Internal Medicine.

The resolution of approval by the Section on Practice of Medicine, American Medical Association, was presented by Dr. James A. Paulin and supported by Dr. S. Marx White, after which it was unanimously adopted.

The historic significance of this action was manifest to all who were present. Within one year after the Regents of the American College of Physicians at the Philadelphia session in 1935 adopted the resolution to underwrite the necessary expense and join with the Section on Practice of the American Medical Association in the organization of a qualifying board for the certification of internists in the United States and Canada, the purpose was accomplished.

The American Board of Internal Medicine comprises nine members with five representatives from the American College of Physicians: Jonathan C. Meakins, O. H. Perry Pepper, David P. Barr, William S. Middleton and G. Gill Richards, and four members representing the Section on Practice of Medicine, American Medical Association: Reginald Fitz, Ernest E. Irons, John H. Musser and Walter L. Biering.

The first meeting of the Board will be held in Chicago, during the month of June, at which time officers and personnel of special committees will be selected, and plans of procedure regarding methods of qualification and certification adopted. All the activities of the Board will be given the fullest publication in the *Annals of Internal Medicine*.

THE IMPORTANCE OF POTASSIUM IN THE TREATMENT OF ADDISON'S DISEASE

THE work of Harrop^{*} and of Allers,[†] and others has shown that the adrenalectomized dog may be kept alive indefinitely without the use of cortical hormone by the administration of sufficient quantities of sodium in the forms of sodium chloride and of either sodium bicarbonate or sodium citrate. Recent work of Allers has indicated that if the potassium intake be kept to a very low level, these animals, maintained on a high sodium intake, will not only live but will show entirely normal plasma electrolyte levels.

Adrenalectomized animals maintained on this high sodium, low potassium regime have shown themselves very much more sensitive to the action of a variety of toxic substances than are normal animals. They have been found to be highly sensitive to the action of insulin, of histamine, and of thyroxine. Important observations have now been published which indicate that they are also highly sensitive to the effect of any increase in the potassium intake.

This sensitivity of the adrenalectomized animal to potassium is especially significant since the effect produced is very similar to the acute crisis seen in the untreated animal following adrenalectomy. The prostration of the animal is accompanied by a fall of serum sodium levels and a rise in serum potassium. The color, viscosity, sedimentation rate and clotting time of the blood resemble similar determinations made on the blood in acute crisis following adrenalectomy. Intravenous injections of large amounts of sodium chloride, sodium bicarbonate and glucose plus large amounts of cortin serve to restore these animals to normal.

The importance of these similarities between the crises produced by increasing the potassium intake and those occurring spontaneously is enhanced by the consideration of data indicating that in Addison's disease in periods of crisis the serum potassium rises as the serum sodium falls. The administration of large doses of cortin tends to reverse these phenomena. It would appear, therefore, that the level of potassium in the serum is as intimately concerned with the mechanism of crisis and as much under the regulation of the cortical hormone as is the level of serum sodium.

The practical application of this principle to the control of Addison's disease has been under investigation in the Mayo Clinic and the results obtained in three patients have been published.[‡] It was found that when the intake of potassium was kept at 1.6 gm per day the sodium and chloride intake could be reduced from such figures as 8.1 gm sodium and 10.9 gm

* HARROP, G. A., SOFFER, L. J., NICHOLSON, W. M., and STRAUSS, M. B. Studies on the suprarenal cortex. IV. The effect of sodium salts in sustaining the suprarenalectomized dog, *Jr. Exper. Med.*, 1935, 11, 839-860.

† ALLERS, W. D. The influence of diet and mineral metabolism on dogs after suprarenalectomy, *Proc. Staff Meet. Mayo Clinic*, 1935, 1, 406-408.

‡ WILDER, R. M., SNELL, A. M., KEPLER, E. J., RYNEARSON, E. H., ADAMS, M., and KENDALL, E. C. Control of Addison's disease with a diet restricted in potassium: a clinical study, *Proc. Staff Meet. Mayo Clinic*, 1936, 1, 273-283.

chloride to 6 gm of sodium chloride daily without seriously altering the levels of serum sodium or serum potassium and without producing clinical evidence of crisis

On the other hand when the patients were in normal condition on a régime of high sodium and chloride and low potassium it was found that if the potassium intake were raised from 1.6 gm to 4 gm there developed a prompt outpouring of sodium and chloride in the urine, the serum sodium fell and symptoms of crisis developed which required active treatment with cortin and intravenous salt

Comparable increases in the potassium intake do not cause any marked change in the serum sodium in normal persons, though if the intake of sodium is high, administration of potassium salts may be followed by some increased urinary excretion of sodium. The action of the natural cortical hormone is apparently protective. Within what limits the administration of cortin will protect against the action of potassium in Addison's disease is not yet fully determined

Wilder has pointed out that the normal diet contains variable amounts of potassium, many common foods such as meat, fish, potatoes, etc yielding as much as 400 mg per 100 gm. It is entirely possible, therefore, that an accidentally increased intake of potassium in the diet may account for some of the hitherto unexplained crises of patients under treatment with a high sodium intake alone. It would seem important therefore to add to the requirements for successful treatment of Addison's disease that dietetic measures be taken to ensure a potassium intake of not more than 1.6 gm a day

REVIEWS

The Diagnosis and Treatment of Variations in Blood Pressure and Nephritis By HIRSHMAN O MOSLEHIAL, M D 616 pages, 15.5 × 24 cm Oxford University Press, N Y 1930, 1931 Price, \$9.00

This volume is divided into two parts, the first dealing with blood pressure and the second with nephritis. In the first part the physiologic dynamics controlling blood pressure, methods of estimating arterial tension, tests for functional efficiency of the circulation, blood pressure as applied to life insurance, the effects of certain everyday habits and daily routine upon the blood pressure, hypotension and hypertension are discussed. The author points out that moderately elevated blood pressures remaining at the same level do not have the same significance as those which progressively become higher. He classifies cases of hypertension according to the elevation of the systolic or diastolic pressure or both, and attributes the first to a large pulse volume or to a general rigidity of the arterial wall, the second to an associated myocardial insufficiency, the last to a primarily increased peripheral vaso-constriction or more commonly to an increase in the tone of the arteries between the heart and arterioles with secondary arteriolar constriction—the cases in this latter group being considered those known as essential hypertension. In regard to the severity of the vascular lesions secondary to or associated with hypertension, the author points out the present confusion in the use of the terms benign and malignant and suggests that better terms would be "mild," "progressive," or "severe." The etiology, symptomatology and treatment of essential hypertension are discussed.

The second part of this volume is devoted to what the author prefers to call Bright's disease, since he feels that nephritis can no longer be considered a disease of the kidney alone, and since furthermore certain conditions included in the non-suppurative renal diseases are not inflammatory in origin. Included in this portion of the book is a discussion of the various types of pathological lesions found, methods of testing renal function, symptoms and signs of impaired function, and treatment. The author has divided treatment into that directed at the pathological lesion and that directed at the symptoms and signs exhibited by the patient. He stresses the point that each patient presents an individual problem. There are separate chapters on edema, anemia, blood pressure and uremia. A classification is offered.

Drs Daniel R Barr, Ernst P Boas, Harold M Frost, C Ward Crampton, Edward C Schneider, Benjamin I Ashe, S Edward King, and James J Short have made contributions to this volume. There is an extensive bibliography.

W S L, JR

Synopsis of Diseases of the Heart and Arteries By GEORGE R HERMANN M D Ph D 344 pages, 13 × 20 cm C V Mosby Company St Louis 1936

This synopsis of cardiovascular disorders is intended for the student and general practitioner. It contains no reference lists but from time to time the names of outstanding investigators are mentioned in the text. It is well indexed. It contains chapters on modern instruments used in the clinical study of the heart, cardiologic roentgenology, and electrocardiography. This book is recommended to those wishing more information on this subject than is to be found in the textbooks on general medicine, and who do not wish to purchase or who have not the time to read one of the more extensive treatises on cardiovascular diseases.

W S L, JR

The Medical Treatment of Gall Bladder Disease By MARTIN E. REHFUSS, M.D., and GUY M. NELSON, M.D. 465 pages, 15 × 24 cm W. B. Saunders Company, Philadelphia 1935 Price, \$5.50

Any comprehensive presentation of the medical treatment of gall bladder disease is timely, for today the results of even expert surgery are often discouraging. Moreover, the mechanism of gall bladder disease is not reversed or changed by surgical treatment, such treatment merely removes the result of a pathological process without affecting its cause. In the light of our present knowledge Rehfuß and Nelson feel that like the diabetic, the chronic biliary sufferer needs an adjustment of his method of living, a recognition of certain dietary procedures, and equally important a systematic check-up of his condition.

The book is well arranged and proceeds in orderly fashion first by stating the problem and then the methods whereby it may be attacked. The physiology of gall bladder activity is reviewed briefly. The important points in the clinical study of the gall bladder patient are described.

The authors believe that the primary problem in the treatment of gall bladder disease is a medical one, although surgical therapy is often necessary as a part of the general program. Certain cases they consider clearly candidates for surgery, but on the other hand they point out that there are exceptions to the rule that gall stones in themselves are an indication for surgical treatment. Careful consideration of the patient's status as a surgical risk is necessary. The clinical similarity to gall bladder disease of pancreatitis, appendicitis, and coronary disease should lead to a careful analysis of clinical data in each case before a final decision is reached.

In discussing the medical treatment, the authors stress the value of considering that in each patient with gall bladder disease one or more etiologic factors are chiefly at play and must be especially combated. The three major etiologic factors they consider to be metabolic defects, infections, and stasis. Diet regulation, the removal of focal infections, the use of vaccines, the employment of duodenal drainage, etc. are more or less appropriate therapeutic methods according to the etiologic factor which predominates in the individual case.

There is a very full discussion of diets, drugs, and special therapeutic methods. General hygiene, rest, exercise, work and diversion are considered from the point of view of the gall bladder patient.

S. M.

The Stomach and Duodenum By GEORGE B. EUSTERMAN, and DONALD C. BALFOUR. 958 pages, 17 × 25 cm W. B. Saunders Company 1935 Price, \$10.00

This book is an excellent example of a cooperative effort on the part of competent men working in unison for the benefit of all of us. They supplement each others' knowledge and in that way are able to present the fundamental facts of diseases of the stomach and duodenum as well as their relationship to other diseases. The gastro-duodenal field is surveyed and brought up to date from all points of view, medical, surgical, physiological, pathological and roentgenological, and the result is an excellent book for internist, surgeon, general practitioner and student.

The authors and contributors have endeavored to confine their discussions to such phases as have more or less direct clinical application, and thus to emphasize the real purpose of coordinated practice, namely, that the benefit of all knowledge, whether clinical, experimental, surgical or pathological, be made available to the individual patient. They have omitted mention of conditions, anomalies, or therapeutic procedures with which they are not sufficiently familiar to cause their opinion to have weight, but on the other hand they have paid the greatest attention to diseases of frequent occurrence such as duodenal ulcer, gastric ulcer, dyspepsia, gastritis, hemorrhage, nutritional disorders, vitamin deficiency states, etc.

The first five chapters may be looked upon as reviews from the historical, physiological, experimental, surgical pathological and pathological points of view. They give the reader that fundamental knowledge upon which a satisfactory clinical approach can be substantially based. The general problem of dyspepsia is classified into four groups. These are the organic, reflex, systemic and functional. Then follows the investigation of the patient. Test meals are discussed and their diagnostic significance evaluated. An illustrated chapter is devoted to roentgenologic diagnosis. Anesthesia for surgical procedures involving the stomach and duodenum are duly considered.

The chapters on duodenal ulcer are excellent. Other phases of duodenal disease such as duodenitis malignant and non-malignant tumors of the duodenum, tuberculosis of the duodenum, chronic dilatation and obstruction of the duodenum, fistulas and injuries of the duodenum, duodenal parasites, diverticula, paraduodenal hernia are considered. Gastric diseases are similarly discussed and it is interesting to see that the subject of gastritis is still a controversial one. Gastric ulcer and cancer, as would be expected, consume many pages. In the chapter on surgical treatment of carcinoma of the stomach, excellent step by step illustrations of various operative procedures are included. The importance of early diagnosis is stressed and the possibility of more and more five year cures is shown to depend upon early diagnosis, proper surgical technic and proper pre- and postoperative care of the patient.

Achlorhydria assumes added significance in view of recent advances in the understanding of it. A chapter is devoted to the medical treatment of inoperable carcinoma of the stomach, a subject upon which we always need enlightenment. The subject of diaphragmatic hernia is discussed. Apparently what was interpreted as an increase in its incidence is due entirely to the awareness that the condition exists and to better diagnosis.

The important subjects of perforation and hemorrhage and their treatments as well as the problem of gastric retention due to duodenal and pyloric obstruction are considered thoroughly. A chapter is also devoted to that moot question of carcinomatous transition of gastric ulcer and another to anemia following operations on the stomach.

It is apparent, therefore, that we have here perhaps the most complete treatise on the stomach and duodenum in the English language. The work is systematically and skillfully arranged following a plan which devotes one-third of the book to general and fundamental considerations, one-third to a discussion of the duodenum in practically all its phases and the final one-third to a similar discussion of the stomach, except for the last chapter which discusses the nature of postoperative pulmonary disease. Both stomach and duodenum are considered in the same sequence.

The bibliography is selective, comprehensive and authoritative. The illustrations are splendid. The book can be highly recommended. S M

Lobar Pneumonia and Serum Therapy By FREDERICK T. LORD, M.D., and RODERICK HERRON, M.D. 91 pages. The Commonwealth Fund, New York. 1936. Price, \$1.00.

This small book, written with special reference to the experience of the Massachusetts Pneumonia Study, will be of interest and value to all those engaged in the care of pneumonia cases. It deals first with the underlying immunological problems and then in a very practical and specific way with such topics as the selection of cases for serum treatment, the technic of typing, the methods and precautions useful in serum therapy, dosage, and reactions. In the last chapter new data are added concerning the results of serum therapy.

The presentation will be clear to any intelligent practitioner and at the same time the observations recorded will be valuable to those fully conversant with the previous literature of this subject. M C P

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the library of the American College of Physicians

- Dr Oliver T Osboine (Fellow), New Haven, Conn —3 books, "What Everyone Ought to Know," "Mouth Infection" and "Evaluation of Symptoms",
Dr Jacob Gutman (Fellow), Brooklyn, N Y —Sixth Supplement to his book, "New Modern Drugs," previously donated to the College,
Dr Jacob Buckstein, New York, N Y —1 book, "Peptic Ulcer",
Lt Col Thomas W Burnett (Fellow), M C, U S A —1 reprint,
Dr Arthur R Elliott (Fellow), Chicago, Ill —18 reprints,
Dr Hubert C King (Fellow), Lakewood, Ohio —1 reprint,
Dr E B Krumbhaar (Fellow), Philadelphia, Pa —16 reprints,
Dr Albert Soiland (Fellow), Los Angeles, Calif —6 reprints,
Dr Pauline Williams (Fellow), Richmond, Va —2 reprints,
Dr W Lawrence Cahall (Associate), Philadelphia, Pa —1 reprint,
Dr Richard J Clark (Associate), Boston, Mass —3 reprints,
Capt James H Forsee (Associate), M C, U S A —5 reprints,
Dr William Freeman (Associate), Worcester, Mass —10 reprints,
Dr Ralph H Kuhns (Associate), Chicago, Ill —1 reprint,
Dr Fred J McEwen (Associate), Wichita, Kan —1 reprint,
Dr G Louis Weller, Jr (Associate), Washington, D C —4 reprints,
Dr F Eugene Zemp (Associate), Columbia, S C —4 reprints
-

The North Carolina State Medical Society met in Asheville May 4 to 6, under the presidency of Dr Paul H Ringer (Fellow), Asheville. A luncheon by North Carolina members of the American College of Physicians was given Tuesday, May 5, in honor of Dr Ernest B Bradley, President of the College, at which 36 Fellows out of a State membership of 66 were present. In addition to President Ringer, four ex-Presidents of the State Society were present, Dr L B McBrayer, Southern Pines, Dr M L Stevens, Asheville, Dr Isaac Manning, Chapel Hill, and Dr Paul P McCain, Sanatorium, as well as Dr Wingate M Johnson, Winston-Salem, President-Elect of the Society, all Fellows of the College. Dr Bradley spoke briefly explaining the progress of the Committee on the Certification of Internists.

Under the Presidency of Dr James E Paullin (Fellow), the Medical Association of Georgia recently held its 87th Annual Session. Dr William B Castle (Fellow), recipient of the Phillips Memorial Award of the American College of Physicians for 1933, delivered the Abner Wellborn Calhoun Lecture.

Dr J Frederick Painton (Fellow), Buffalo, N Y, has been appointed Associate in Medicine at the University of Buffalo School of Medicine for the academic year, 1936 to 1937.

Dr A U Desjardins (Fellow) Rochester, Minn, is Chairman of the American committee in charge of the First International Congress on Fever Therapy to be held at Columbia University, New York City, September 29 to October 3, 1936. The subjects to be discussed will include physiologic and pathologic changes as well as the

treatment of gonorrhea, both in the male and in the female, gonorrheal and non-specific arthritis, syphilis in its various stages, neurologic conditions such as multiple sclerosis, chorea, paresis, tabes, skin diseases, etc. This meeting will be held under the Chairmanship of Baron Henri de Rothschild of Paris France. There is a French committee headed by Professor d'Aisonval as honorary President and Professor Abram as Chairman. There is a national European committee with members representing various European countries.

An abstract of the papers will be published in the volume of the transactions in English, German and French. Information regarding the conference may be obtained from the Secretary, Dr. William Bierman, 471 Park Avenue, New York N. Y.

Dr. William Nimch (Fellow), Mexico, D. F., has been elected President of the Mexican Chapter of the National Society for the Advancement of Gastro-enterology.

Dr. Nimch also was recently and unanimously elected a member of the National Academy of Science.

Dr. Archibald L. Hoyne (Fellow), Clinical Professor of Pediatrics, Rush Medical College, and Associate Clinical Professor of Pediatrics, School of Medicine of the Division of the Biological Sciences, University of Chicago, addressed the Northern Ten-State Medical Meeting at Fort Wayne, Ind., in April on "Progress in the Management of Contagious Diseases."

He also addressed the Nebraska State Medical Meeting at Lincoln, during April, on "The Treatment of Meningococcic Meningitis Without Intraspinal Therapy," and the Iowa Public Health Association's meeting at Des Moines, on April 28, on "Diphtheria." On May 29 he addressed the Iowa State Medical Meeting at Des Moines on "Meningococcic Meningitis."

Dr. C. C. Burlingame (Fellow), Hartford, Conn., as Chairman of the Committee on Public Education of the American Psychiatric Association, recently announced the election by the Board of Examiners of that organization, of Dr. Kenneth Appel (Associate), Philadelphia, Pa.

Dr. Howard M. Jameson (Fellow), Wilkes-Barre, Pa., has accepted a Public Health appointment in Great Britain.

Newly elected Fellows of the American College of Physicians of Puerto Rico gave a dinner on April 28 in honor of the College Governor of the Island, Dr. R. M. Suarez. Dr. Suarez presented a report upon the Twentieth Annual Session of the College held in Detroit, at which he was in attendance. There was a round table discussion in regard to the College, its policies and the further development of its membership in Puerto Rico. Action was taken toward organizing a local unit with the purpose of furthering the aims and objects of the College and its scientific activities in the Island.

Under the Presidency of Dr. F. M. Pottenger (Fellow), Monrovia, the Twentieth Annual Scientific Session of the Association for the Study of Internal Secretions was held in Kansas City, May 11 to 12. Among members taking part in the program were

- Dr E L Sevringhaus (Fellow), Madison, Wis (with R K Meyer)—“Gonadotropic Inhibitory Substances in Blood of Women and Monkeys After Anterior Pituitary Therapy”,
- Dr J B Collip (Fellow), Montreal, Que (with Hector Mortimer, Percy Wright, Carl Bachman)—“The Hormone Relationship Between the Female Organs of Sex and the Nasal Mucous Membrane” and “Further Studies in Anterior Pituitary Physiology”,
- Dr Henry J John (Fellow), Cleveland, Ohio—“The Interrelationship Between the Pancreas and Other Endocrine Organs in Diabetes”
- Dr Hans Lissner (Fellow), San Francisco, Calif—“Two and One-Half Years' Observation of a Patient with Cushing's Disease, Following Removal of a Pars Intermedia Adenoma”,
- Dr W O Thompson (Fellow), Chicago, Ill (with N J Heckel, A D Bevan, E R McCarthy and P K Thompson)—“The Treatment of Undescended Testicles with an Anterior Pituitary-Like Substance”,
- Dr L G Rowntree (Fellow), Dr J H Clark (Fellow) and Dr N H Einhorn (Fellow), all of Philadelphia (with Arthur Steinberg, Philadelphia, and A M Hanson, Faribault, Minn)—“The Role of the Thymus Gland in Growth and Development”,
- Dr Homer P Rush (Fellow), Portland, Ore—“Three Cases of Macrogenitosomia”,
- Dr Daniel L Sexton (Fellow), St Louis, Mo—“Treatment of Sexual Underdevelopment in the Human Male with Pregnancy Urine Extract Further Report”,
- Dr Matthew Molitch (Associate), Jamesburg, N J (with Sam Poliakoff)—“Hypothyroidism in Behavior Problems”
-

Dr Joseph C Doane (Fellow), Medical Director of the Jewish Hospital of Philadelphia, will give a short course in hospital operation in the Summer School of Hotel Administration at Cornell University, June 29 to July 11. The course, planned as a “refresher” course for those already engaged in hospital work is a “unit” course, which means that students enrolled will devote all their study time exclusively to the study of hospital problems

The Philadelphia County Medical Society, during the week of April 20 1936, conducted its First Annual Postgraduate Institute. Authorities in their respective fields offered postgraduate lectures relating especially to cardiovascular and renal diseases. Admission was open to all interested physicians not only locally but throughout the eastern portion of the country. The following Fellows of the College were members of the Committee on the Postgraduate Institute: Dr E J G Beardsley, Dr Edward L Bortz, Dr Willis F Manges, Dr H K Mohler and Dr William D Stroud

Dr David P Barr (Fellow) and Dr Sinclair Luton (Fellow) both of St Louis, addressed the annual meeting of the Missouri State Medical Association at Columbia, Mo on “Nature and Treatment of Obesity” and “The Clinical Use of Digitalis Variables Encountered,” respectively

Dr William Devitt (Fellow) Allenwood Pa, is President of the Pennsylvania Tuberculosis Society, succeeding Dr Charles Howard Marcu (Fellow), Pittsburgh

Under the Presidency of Dr Herbert L Bryans (Fellow), Pensacola, the 63rd Annual Meeting of the Florida Medical Association was held on the S S Florida, April 27 to 29, on a cruise to Havana

Dr Willis F Manges (Fellow), Philadelphia, presented the Russell D Carman Memorial Lecture, sponsored by the Minnesota Radiological Society, during the annual session of the Minnesota State Medical Association at Rochester, Minn, early in May. Dr Manges' title was "Foreign Bodies and the Use of X-Ray Examination in Their Localization and Removal"

Dr James Alex Miller (Fellow) has been appointed Administrative Consultant in Tuberculosis to the New York City Department of Hospitals

A reception and testimonial dinner was tendered to Dr Andrew P Biddle (Fellow), Detroit, on April 1 by the Wayne County Medical Society and the Detroit Dermatological Society in recognition of his completion of fifty years in the practice of medicine. Dr Biddle is Emeritus Professor of Dermatology at Wayne University, College of Medicine. He was President of the Detroit Board of Education in 1925, President of the Detroit Library Commission in 1931, Charter member of the Wayne County Medical Society and was the first Editor of the Journal of the Michigan State Medical Society. He has also acted as President of the State Society, President of the Detroit Academy of Medicine and President of the American Dermatological Society

Dr Robinson Bosworth (Fellow), Rockford, has been elected President of the Illinois Tuberculosis Society

Dr Andrew C Ivy (Fellow), Chicago, has been named Secretary of the American Physiological Society.

Under the Presidency of Dr Robert A Peers (Fellow), Colfax, Calif, the 65th annual meeting of the California Medical Association was held at Coronado, May 25 to 28. Dr Jacob J Singer, St Louis, Dr Harry H Wilson, Los Angeles, Dr F M Pottenger, Monrovia, Dr Philip H Pierson, San Francisco, all Fellows of the College, were among the speakers on the program

Dr Ralph A Kinsella (Fellow), St Louis, delivered the annual oration in medicine before the Illinois State Medical Society at its meeting in Springfield, May 19, his title being "The Career of a Heart"

Dr George W Covey (Fellow), Lincoln, Nebr, was installed as President of the Nebraska Medical Association at its 68th annual meeting during April

Dr Peter Irving (Fellow), New York City, is Secretary of the Medical Society of the State of New York

Dr Earl B McKinley (Fellow), Washington, D C, has been named Vice-President of the American Association of Pathologists and Bacteriologists

Dr Charles F Martin (Master) for many years Dean of the Faculty of Medicine of McGill University, Montreal, will retire August 31, having reached the retirement age in effect at that institution

Dr Albert Grant Fleming, Professor of Public Health and Preventive Medicine and Director of the Department, has been appointed Dean to succeed Dr Martin

A newly established position of Associate Dean will be filled by J C Simpson, LL D, Secretary of the Faculty of Medicine and Chairman of the Committee on Physical Education

OBITUARIES

DR CLARENCE EUGENE SIMONDS

Clarence E Simonds was born February 13, 1874, in the town of Mansfield, Conn, a son of William E and Mary (Lee) Simonds

He was educated in the common schools of Mansfield and graduated from Willimantic High School in 1893 After teaching for a year he entered the medical school of New York University, finishing the course there in 1897 Following this he did postgraduate work at New York Post-graduate Medical School and Hospital

He practised his profession in Danielson and South Coventry, Conn, before beginning to practice in Willimantic in 1903, where he has remained until about a year ago when failing health caused him to give up all active work He served as health officer of the town of Windham and was medical examiner for the towns of Windham, Scotland and Hampton for many years until ill health compelled him to resign

He was formerly Attending Physician, St Joseph's Hospital, Chief Physician and President of the Medical and Surgical Staffs, Windham Community Memorial Hospital, ex-president and ex-secretary of Willimantic City Medical Society, ex-president of Windham County Medical Society, a member of the Connecticut State Medical Society and of the American Medical Association He was also a member of the Willimantic Chamber of Commerce and past president of the Exchange Club He became a Fellow of the American College of Physicians in 1930

At the time of his death he was president of the professional staff of the Windham Community Memorial Hospital

HENRY F STOLL, M D, F A C P,
Governor for Connecticut

DR ARTHUR D HOLMES

Arthur David Holmes, M D, C M, Detroit, Michigan, died after a short illness, February 20, 1936

Dr Holmes was born in Chatham, Ontario, in 1863 He graduated from McGill University, Faculty of Medicine, in 1889, and then started practice in Detroit Very early he confined his work to pediatrics He spent the year 1902-1903 in London and Vienna doing graduate work in the diseases of children

He held numerous teaching and hospital appointments Attending Physician, Children's Free Hospital, 1905-1916, Attending Physician, Woman's

Hospital and Infants' Home, 1907-1916, Consultant to both of these institutions to the time of his death, Clinical Professor of Pediatrics, Detroit College of Medicine, 1913-1916. He held membership and office in many medical societies: Wayne County Medical Society (President in 1910, and a Trustee from 1910 to 1930), Michigan State Medical Society, American Medical Association, Detroit Academy of Medicine (President, 1901), Mississippi Valley Medical Association (Vice-President, 1912), Central States Pediatric Society. Dr. Holmes was one of the very early members of the American College of Physicians, having taken Fellowship in 1917. He was also a Director of the Equitable Trust Company, Charles W. Warren Company, and the Central West Casualty Company. In social organizations he held membership in the Detroit Club, the Wittenagencote Club, and the Detroit Country Club.

Dr. Holmes had been a widower for many years, and is survived by two daughters, Mrs. Ernest G. Davis and Miss Agnes Holmes of Detroit.

Dr. Holmes' death is a great loss to the medical profession of the city and state. He was one of the earliest to confine his work to pediatrics, and for many years was an active teacher in the college and hospitals of the city. As an able clinical teacher, his work became the inspiration for many of our younger pediatricians. A gentleman of broad culture and great personal charm, he enjoyed a wide social acquaintanceship in the city. Organized medicine also owes a great debt to Dr. Holmes, for it was during his presidency in 1910 and under his inspiring guidance, that the Wayne County Medical Society first purchased and became quartered in a building of its own, marking an important step in the growth and prosperity of the Society. The profession will miss greatly his genial friendship, and his able professional counsel.

HENRY R. CARSTENS, M.D., F.A.C.P.,

Governor for Michigan

DR. WEBSTER STANLEY SMITH

Dr. Webster Stanley Smith (Associate), Dayton, Ohio, died January 30, 1936, of arteriosclerosis, at the age of 79. Dr. Smith was born in Dayton, November 13, 1856. He attended the public schools and graduated from the Medical College of Ohio in 1880. For many years he was connected with the Miami Valley Hospital as a member of the department of medicine and as instructor to nurses in diseases of the chest. He was a member and past president of the Montgomery County Medical Society, a member of the Ohio State Medical Society, the Mississippi Valley Medical Society, the American Medical Association, and had been an Associate of the American College of Physicians since 1925.

MINUTES OF THE BOARD OF REGENTS

DETROIT, MICH

March 1, 1936

A regular meeting of the Board of Regents was held at the Book-Cadillac Hotel, Detroit, March 1, 1936, with the following present James Alex Miller, President, Ernest B Bradley, President-Elect, David P Barr, Second Vice-President, William Gerry Morgan, Secretary-General, William D Stroud, Treasurer, Walter L Bierring, John H Musser, O H Perry Pepper, Francis M Pottenger, Luther F Warren, William J Kerr, Roger I Lee, Sydney R Miller, George Morris Piersol, G Gill Richards, James B Herrick, Jonathan C Meakins, James H Means, James E Paullin, Maurice C Pincoffs, Charles H Cocke, and Dr Alfred Stengel, Chairman, College Headquarters Committee, and Mr E R Loveland, Executive Secretary, acting as secretary of the meeting, with Dr James Alex Miller, of New York City, President of the College, presiding

The Executive Secretary read abstracted Minutes of the meeting of the Board of Regents held in Philadelphia December 15, 1935, which were approved as read

President Miller in preliminary remarks referred with regret to the death of Dr Charles G Jennings General Chairman of the Twentieth Annual Session, to two main subjects to be discussed later in the meeting, namely, the matter of a permanent home for the College and the certification of internists by the American Board of Internal Medicine, and to the remarkably satisfactory manner in which the Executive Offices had functioned during the past year

The Executive Secretary then presented a communication from Professor M Fernandez of Marquette University School of Medicine, Milwaukee, inviting, on behalf of Prof Dr Gustavo Pittaluga, Madrid, Spain, President of the III International Congress on Malaria to be held there October 12 to 18, 1936, some representative of the College to attend the Congress

On motion by Dr Bierring, seconded by Dr Pepper, and regularly carried, it was

RESOLVED, that the incoming President, Dr Ernest B Bradley, may designate any Fellow of the College whom he finds is going to attend this Congress to act as the official delegate of the American College of Physicians

Dr Ernest B Bradley, Chairman of the Committee on Public Relations presented the following resignations, which were acted upon by resolution

Associates

Bernard G Efron	New Orleans, La
Walter S Lucas	Wynnewood, Pa
Jenaro Suarez	San Juan, P R

Fellows

W L Holman	Toronto Ont
Lester J Williams	Baton Rouge, La

RESOLVED, that the resignations of the three above named Associates and two Fellows be accepted

Dr William Gerry Morgan, Secretary-General, presented the following resolution, which was unanimously adopted, on the death of Dr Charles G Jennings (Master), including its being spread upon the Minutes of this meeting and a copy of it being sent to Dr Jennings' son, Dr Alpheus Jennings

IN MEMORIAM

CHARLES GODWIN JENNINGS

WHEREAS Through the death of Charles Godwin Jennings on January 9th, 1936, the American College of Physicians has lost one of its earliest and most distinguished members

Dr Jennings was elected to Fellowship in 1916 at the first annual meeting of the College held in New York City He was the second Fellow to be elected Master

During the twenty years of his membership as Fellow and Master, Dr Jennings took an active part in shaping the development of the College

He was President of the American Congress on Internal Medicine 1925 to 1926, at that time an integral part of the College He served for many years as Governor of the College for the State of Michigan, and as such built up a large and enthusiastic State membership On his retirement from the office of Governor, he was elected to the Board of Regents and served in this capacity until 1930 He was elected Second Vice-President of the College in 1931 and served until 1933, when he was made First Vice-President Dr Jennings was returned to the Board of Regents in 1935 for a term of three years

At the time of his death, Dr Jennings was General Chairman for the Twentieth Annual Meeting of the College

Dr Jennings by his broad vision, keen judgment and wise counsel had won the confidence and esteem of those with whom he had worked for so many years

THEREFORE BE IT RESOLVED that we express our deep sorrow for the loss of this true physician and wise counselor

The Executive Secretary, Mr Loveland, presented cases of failure to take up election, delinquency, and failures to qualify for Fellowship Two names were discontinued on the Fellowship Roster for failure to take up election, 14 Associates were dropped from the roll for failure to qualify for Fellowship within five years of their election to Associateship, as required by the By-Laws, 7 Fellows and 5 Associates were dropped from the roll because of delinquency of two years or more

Reporting upon the candidates elected to Associateship in 1931 and whose term of Associateship expires with the 1936 Annual Session, the Executive Secretary presented the following analysis

78 Qualified for Fellowship
2 Died
4 Resigned
1 Failed to take up election
16 Were rejected or dropped

101 Total elected 1931

77 2% qualified for Fellowship, 22 8% failed ever to become Fellows

Dr William Gerry Morgan, Secretary-General, reported the deaths of the following members since the last meeting of the Board of Regents

Master

Charles Godwin Jennings	Detroit, Mich	January 9, 1936
-------------------------	---------------	-----------------

Fellows

Henry Wald Bettmann	Cincinnati, Ohio	December 5, 1935
Thomas C Chalmers	Forest Hills, N Y	November 16, 1935
William Krauss	Meridian, Miss	December 21, 1935
George Washington McCaskey	Fort Wayne, Ind	December 30, 1935
Stephen Roman Pietrowicz	Chicago, Ill	January 12, 1936
Hubert Schoonmaker	Clifton Springs, N Y	October 21, 1935
Charles D Steinwinder	San Antonio, Tex	

Associates

John Leonard Eckel	Buffalo, N Y	November 26, 1935
Henry Finlay Hyndman	Wichita, Kan	October 31, 1935

Dr Morgan also reported the following list of Fellows who have become Life Members since the last meeting of the Board of Regents This made a total of sixty-one Life Members, including the late Dr John Phillips

Lewis Beals Bates	Ancon, Canal Zone
Casper H Benson	Columbus, Ohio
Donald Gregg	Wellesley, Mass
James Rae Arneill	Denver, Colo
Thomas Fitz-Hugh, Jr	Philadelphia, Pa
C Charles Burlingame	Hartford, Conn
Noble Wiley Jones	Portland, Ore
Cecil M Jack	Decatur, Ill
Anna Weld	Rockford, Ill
Roy M Van Wart	Descanso, Calif (formerly of New Orleans)
Estes Nichols	Portland, Maine
William Henry Watters	Coconut Grove, Miami, Fla

Dr George Morris Piersol, Chairman of the Committee on Credentials reported that the Committee had held two meetings, one at the College Headquarters in Philadelphia on February 2 and one at Detroit on March 1 He distributed to the Board of Regents a mimeographed list of the recommendations for election both to Fellowship and Associateship from the meeting of February 2 An analysis of this list follows

Recommended for election to Fellowship	
Advancement for Associateship	39
Direct election to Fellowship	15
	<hr/> 54
Recommended for election to Associateship first	1
Deferred for further investigation, maturity etc	10
Rejected	1
	<hr/> 66

Of those recommended for election directly to Fellowship, the majority were members of the Medical Corps of the U S Army and U S Navy

An analysis of the recommendations of the Committee on the Associate candidates considered February 2 was as follows

Recommended for election to Associateship	
From regular list	48
From Fellowship list	1
	<hr/>
	49
Deferred for further consideration	11
Rejected	6
	<hr/>
	66

Dr Piersol having insufficient time to mimeograph the recommendations of March 1, read the list of recommendations to the Board. His analysis of the candidates considered on March 1 was as follows:

Recommended for election to Fellowship	
Advancement from Associateship	40
Direct elections to Fellowship	11
	<hr/>
	51
Recommended for election to Associateship first	1
Deferred for further investigation maturity, etc	4
Rejected	3
	<hr/>
	59

An analysis of the candidates considered for Associateship on March 1, follows:

Recommended for election to Associateship	41
Recommended for election directly to Fellowship	2
Deferred for further consideration	2
Rejected	7
	<hr/>
	52

The combined lists of recommendations from the meetings of February 2 and March 1, both for Fellowship and Associateship, follow. On motion by Dr Piersol seconded by Dr Bradley and regularly carried, it was

RESOLVED, that the following 105 candidates for Fellowship and 92 candidates for Associateship shall be and are hereby elected to membership in the respective classes indicated.

The complete list of elections was published in the March, 1936, issue of this journal.

Dr Piersol, on behalf of the Committee on Credentials, presented two cases for advice and direction from the Board of Regents: (1) the case of a Fellow who resigned some years ago and who now is interested in being reinstated, but at a minimum of expenditure. After thorough discussion of the case, the Board of Regents, by resolution, directed that it shall be the policy in such cases to require the payment of all delinquent dues and to have the support and recommendation of the Governor of the district for reinstatement. The Board expressed itself as unfavorable to establishing a precedent of permitting members to leave and reenter the College at will without any obligation in the meantime. The only other method of regaining membership would be through an original proposal and reentry according to the present requirements, (2) the case of a former Fellow who subsequently became a Fellow of the American College of Surgeons and who specialized thereafter particularly in Obstetrics, although he is highly accomplished also in Internal Medicine. This member had resigned his Fellowship in the American College of Physicians because he understood it was the policy of the College not to include in its membership those engaged in obstetrical practice, or those who had become members also of the American College of Surgeons. This case was presented to determine whether the Board of Regents would consider reinstatement to active Fellowship in this College. A resolution was adopted re-

iterating the fact that the policy of the American College of Physicians remains the same in this respect as in the past, and that consequently as long as the candidate in question remains a Fellow of the American College of Surgeons and is not confining his work mainly if not exclusively, to Internal Medicine, the case cannot be reopened.

Dr Alfred Stengel, Chairman of the temporary Committee on the College Headquarters, reported that after his Committee had considered the matter, it had come to the conclusion that it was of such importance that the broad question of principle should be passed upon by the Regents before the Committee engaged anyone to draw up detailed plans. Therefore, he reported only upon the general proposition of a College Headquarters. There were two problems: first, whether the College wishes or requires a building for its headquarters, leaving rental considerations altogether out of mind, and, second, if they do feel that they should have such a building or headquarters, how far the Board of Regents of the College would like to go in the matter of expenditure. In regard to the question of the desirability, it has been the feeling of all the members of the Committee perhaps with some slight amendment in the way it was presented that it seems desirable that the College should have a dignified place wherever the headquarters of the College will be located, where Fellows of the College, as they may perhaps be going through that center, would find occasion to make visits either to obtain information, to arrange programs or to stop casually. He had obtained information from the Executive Secretary that aside from the meetings of the Regents and Governors at the College Headquarters, from time to time, there are perhaps one hundred and fifty or more visitors from the membership of the College every year who come to the headquarters for one purpose or another. The universal comment of visitors is that the College Headquarters is inadequate and inferior. He said there are all kinds of reasons that may be advanced as to why the College should have a central headquarters, but that he was passing over those to consider the question of finances. The Committee had determined that the cost of operating its headquarters including the loss of interest on the investment, maintenance, light, heat, taxes, etc., would total about \$8,000.00 per annum. This was all predicated on the erection of a building that would cost approximately \$100,000.00. Calculating the amount of space that the Executive Offices reasonably would require in the building where they are now located, the cost would be approximately \$7,800.00 per annum, or a difference only of \$200.00 between offices in an ordinary office building and headquarters in a dignified, individual home.

Dr Stengel reported that his Committee had surveyed many properties in the vicinity of the present College Headquarters, and had found one location, a vacant lot in a very desirable neighborhood, convenient to one of the large academic medical centers, to a first-class hotel and to transportation, which could be obtained for about \$30,000.00. The Committee felt that an appropriate headquarters could be erected and furnished for an additional \$70,000.00, as an outside figure. An architect, without charge to the College, had made several sketches and submitted different kinds of plans, making the estimate within the amount indicated above, and providing for materials of the best quality and a fireproof structure. Dr Stengel described the architect's plans, which were presented purely as a working basis and a theoretical possibility, that called for a Georgian building of two stories with an unfinished third floor, of construction permitting for adding additional floors if in future years such would be required. The type of architecture was in keeping with the surrounding buildings.

The Committee recommended to the Board of Regents favorable consideration of a permanent headquarters building erected and furnished in Philadelphia at a cost not to exceed \$100,000.00.

After wide discussion, a resolution was adopted to the effect that it was the sense of the Board of Regents that they approve in principle the program outlined by the Committee, but that final action be deferred until after a conference with the Board of Governors and until further and more specific details can be obtained.

Even after the adoption of this resolution, there was extended discussion in which it was brought out that the location considered was not far removed from the new mun station.

of the Pennsylvania Railroad and the new U S Post Office. The location was thought by some to be one that would be definitely appreciating in value as years go by.

The consensus of opinion was that the College should be conservative, should not expend an unnecessary amount, other than reasonably required, that it should take into consideration various uses for the College funds, but that if an appropriate College Headquarters of dignified character and adequate facilities could be provided, it would be a tangible evidence of its existence, that it would be a convenience to its members, and would provide better facilities for the proper functioning of the Executive Offices.

The discussion led also to a consideration of the initiation fee for Fellowship, it being suggested that as soon as possible, the Board should take under consideration a reduction of the present initiation fee of \$80.00. There has been an erroneous idea that the initiation fee was \$100.00, to which the annual dues have to be added. As a matter of fact, the initiation fee is but \$80.00 a year for practicing clinicians, with a gradual reduction, according to salary, for those employed as medical teachers or research workers in non-profit institutions.

At the end of the discussion, Dr. Stengel concluded with the following remarks:

"I have tried to present this matter as objectively as possible, without going into some of the details that have been brought forward. The College has accumulated funds at a fairly rapid rate, due in great measure to its careful administration. If you can now invest some of that money to house yourself and pay your own headquarters rent instead of leaving it invested in funds producing income which you might be spending in other ways, your situation will be exactly the same. You are going to spend the same amount of money for rental as you will be spending upon this new building. It leaves you just where you are.

"The second proposition that immediately suggests itself is that the College could afford to reduce its present initiation fee. One of my fears is, and I am speaking as an 'ex-,' is that the College will get too many members, which will kill it, and at present you are either right on the edge of or you have already accomplished a stricter method of surveillance of those who are candidates, which will keep out undesirables. If you had eliminated your initiation fee five years ago and persons could have come into the College without an initiation fee, but by merely paying \$15.00 a year dues, you would have had a much louder outcry at your door for admission on the part of undesirables. Your Committee on Credentials would have had a much harder job, and no matter how hard they worked, they would have let in a lot more undesirables than they did let in. Your initiation fee, in a sense, has stood as a guardian for the College. Now, with the proposition of a strict examination for admission to the College, that reason for an initiation fee will no longer exist in the same manner, and I think that this proposition makes it entirely possible to take some of your surplus and put it into a building which will make for a sense of stability and a sense of dignity, rather than to be merely a showplace.

"In my earlier report I mentioned the number of people who stop at the headquarters. Although that is a very unimportant thing and no one, I would think, would regard it otherwise, yet when one hundred and fifty men come along and say with disappointment, 'Is this where you live?'—well, that is one hundred and fifty men in an organization who go away and tell a sundry other one hundred and fifty men what they think of it. There is no strong argument for putting up a palace, but I think a dignified building that lends a sense of stability to an organization is a very important thing, and I think that financially you can well afford to do it, and, after you have got it, you can well afford to reduce your initiation fee and, perhaps, other fees as well."

Dr. Walter L. Biering, as Chairman of the joint Committee on the Certification of Internists, distributed copies of his report, which was as follows:

REPORT OF JOINT COMMITTEE

(American Board of Internal Medicine)

DETROIT, MICH.,
March 1, 1936

TO PRESIDENT JAMES ALLEN MILLER

AND

MEMBERS OF THE BOARD OF REGENTS,
AMERICAN COLLEGE OF PHYSICIANS

Since the report of this Joint Committee presented to the Regents at the meeting in Philadelphia, December 15, 1935, the further developments in the formation of the American Board of Internal Medicine are reported herewith.

1 An application in due form was submitted to the Advisory Board for Medical Specialties, which functions in connection with the Council on Medical Education and Hospitals of the American Medical Association, for approval of the organization of the American Board of Internal Medicine.

This application was accompanied by a copy of the proposed Articles of Incorporation which embodied the Constitution, a copy of the By-Laws, which includes the requirements and methods of Certification of Specialists in Internal Medicine and a copy of the application blank.

Within a short time, advice was received from Dr. Paul Titus, the Secretary of the Advisory Board for Medical Specialties, that its Committee on Credentials and Qualifications had reported favorably on the application and so recommended to the Executive Committee of the Advisory Board for its meeting in Chicago on February 16, 1936.

2 The Joint Committee met in Chicago on Sunday, February 16, 1936, at which time certain minor changes were made in the Articles of Incorporation and the By-Laws, which were then submitted in corrected form to the Executive Committee of the Advisory Board of Medical Specialties, members Irons, Middleton and Bierring appearing for the Joint Committee.

The Executive Committee of the Advisory Board approved the formation of the American Board of Internal Medicine and transmitted its action to the Council on Medical Education and Hospitals of the American Medical Association at its meeting on Monday, February 17, 1936, which Council endorsed the action of the Advisory Board.

It was stated by both of the above bodies that final official action and approval would be withheld until a meeting of the entire Advisory Board for Medical Specialties and that of the Council on Medical Education and Hospitals in Kansas City, Mo., May 10 to 15, 1936, during the annual session of the American Medical Association.

If the Regents of the American College of Physicians, during this session, can approve the steps thus far taken in the formation of the American Board of Internal Medicine, the further official approval of the Section on Practice of Medicine of the American Medical Association can be obtained at its executive meeting on May 15, 1936, at Kansas City. After this has been accomplished, all the requirements of organization will have been complied with and the American Board of Internal Medicine will then be ready to begin operations.

At the meetings in Chicago, February 16 and 17, 1936, the Advisory Board for Medical Specialties and the Council directed that the Articles of Incorporation be filed in a Court of Record and this was accordingly done at Des Moines (Polk County), Iowa, on Friday, February 28, 1936.

The three required witnesses to the document, residents of Des Moines, were Dr. Tom B. Throckmorton, Governor for Iowa of the American College of Physicians, Dr. Fred Moore, Member, Council on Medical Education and Hospitals of the American Medical Association, and Dr. Walter L. Bierring, Member of the Joint Committee.

The purpose of filing these Articles in Iowa seemed advisable because of more favorable regulations in this State for non-profit sharing corporations. A special filing fee, an annual report and registration are not required as is the custom in some of the other States.

Because the Articles are filed in Iowa does not imply that the place of business of the Board shall necessarily be in Iowa

It will be noted by the accompanying copy of the Articles of Incorporation (Constitution), that the American Board of Internal Medicine is composed of nine members, five of which shall be Fellows of the American College of Physicians, and four shall be representative of the Section on Practice of Medicine of the American Medical Association

Previous to the meeting of the Advisory Board for Medical Specialties in Chicago on February 16, 1936, Dr James Alex Miller, by virtue of his authority as President of the American College of Physicians, submitted to the secretary of the Advisory Board, Dr Paul Titus, the names of Drs Meakins, Pepper, Middleton, Barr and Richards to represent the American College of Physicians, and in like manner, Dr William J Kerr, as Chairman of the Section on Practice of Medicine of the American Medical Association, the names of Drs Fitz, Irons, Musser and Bierring to be members of the first American Board of Internal Medicine

The By-Laws include the requirements for special training in Internal Medicine and procedure of Certification, which incorporate the report of the special committee appointed at the meeting on December 14, 1935—Drs Meakins, Fitz, Irons and Middleton

The Founders Group or Charter Members which are to be certified without examination within the period until July 1, 1937, will be more limited in number than at first proposed

The Joint Committee expects to hold a meeting tomorrow, Monday, March 2, 1936, at 4 00 p m, at which time further details of organization of the American Board of Internal Medicine, as well as Examination and Certificate procedure, will be considered

It now seems probable that the first (Part I) Written Examination will be held in December, 1936, and the first (Part II) Practical or Clinical Examination will be conducted at or near the time and place of the Annual Session of the American College of Physicians in 1937

The Joint Committee at this time desires to record its appreciation of the constant encouragement and valuable advice given so freely at all times by Dr James Alex Miller, President of the American College of Physicians, Dr William J Kerr, Chairman of the Section on Practice of Medicine of the American Medical Association, and particularly Mr E R Loveland, Executive Secretary of the American College of Physicians, for many important suggestions and faithful cooperation during the formative period of the American Board of Internal Medicine

Respectfully submitted—WALTER L BIERRING, *Chairman*

JONATHAN C MEAKINS }
O H PERRY PEPPER }
WM S MIDDLETON }
DAVID P BARR }
JOHN H MUSSER }
G GILL RICHARDS }

*American College
of Physicians*

ERNEST E IRONS

REGINALD FITZ

WALTER L BIERRING

} *Section on Practice of
Medicine, American
Medical Association*

In submitting this report, Dr Bierring asked members of the Board to read the material over carefully in preparation for a further discussion of the matter at the next meeting Dr Bierring's report was received with applause and a resolution adopted accepting the report with the profound thanks of the Board of Regents Thereupon, Dr Bierring stated that the formation of this Board has gone forward in stages, and that his Committee feels that at this time the steps that have been taken thus far should have the sanction of the Board of Regents of this College It was suggested, however, that action be deferred until after the reports might be further studied and also examined by the Board of Governors

Adjournment

Attest E R LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF REGENTS

DETROIT, MICH

March 3, 1936

The second meeting of the Board of Regents, during the Twentieth Annual Session at Detroit, was held Tuesday, March 3, 1936, at the Book-Cadillac Hotel, convening at 12 15 o'clock, with Dr James Alex Miller, President, presiding, with the following present James Alex Miller, President, Ernest B Bradley, President-Elect, Arthur R Elliott, First Vice-President, David P Barr, Second Vice-President, William Gerry Morgan, Secretary-General, William D Stroud, Treasurer, Walter L Bierring, John H Musser, O H Perry Pepper, Luther F Warren, William J Kerr, Roger I Lee, Sydney R Miller, George Morris Piersol, G Gill Richards, James B Herrick, Jonathan C Meakins, James H Means, James E Paulin, Maurice C Pincoffs, Charles H Cocke, and with Mr E R Lovcland, Executive Secretary, acting as secretary of the meeting

The reading of abstracted Minutes of the previous meeting was dispensed with

Dr Charles H Cocke, Chairman of the Board of Governors, reported the following resolutions received from the Board of Governors at their meeting the day previous

RESOLVED, that the Board of Governors recommend to the Board of Regents, and such other Officers as may be concerned in the selection of the time for the Annual Meeting, to hold future Annual Sessions at as late a date in April as consistent with the convenience of those in the City in which the meeting will be held

Chairman Miller ruled that this resolution merely will be entered on the Minutes as a record of a communication to be considered by those in charge of setting the date of the next meeting

RESOLVED, that the Board of Governors suggests to the Board of Regents the desirability of having the By-Laws amended to provide for the appointment of alternates for Governors who cannot attend the Annual Sessions

It was explained by Dr Cocke that there were three provisions allowed to sit by unanimous vote of the Board of Governors at the meeting of that Board the preceding day. He felt that every constituency has a right to representation, and since there is no constitutional provision for it, the Board of Regents should take under consideration proper amendments providing for the same

On motion by Dr Piersol, seconded by Dr Bradley, and regularly carried, it was

RESOLVED, that the Board of Regents instruct the Committee on Constitution and By-Laws to draw up proper amendments providing for alternates for Governors who cannot attend the Annual Sessions, and that the proposed amendments be presented in accordance with present provisions of the Constitution and By-Laws

RESOLVED, that the Board of Governors shall express to the Board of Regents their approval of the project for the acquisition of a permanent College home and headquarters, and, further, recommend that the Board of Regents proceed immediately on the project

Chairman Miller reported that he had been present at the meeting of the Board of Governors at which the matter of the College Headquarters was discussed, and that it was quite impressive, since it was unanimous, with the exception of one Governor, in revealing what the general fellowship of the College feels about it. There had not been a single vote from the Board of Governors in the negative, although in the discussion at least one had indicated some opposition

RESOLVED, that the Board of Governors express to the members of the Board of Regents their keen appreciation and thanks for the Dinner tendered them on March 1

It should here be recorded that the members of the Board of Regents, as individuals, tendered a Dinner to all members of the Board of Governors who could be present on the evening preceding the opening of the Annual Session. Matters of general interest to the College and to each Board were freely discussed

Chairman Miller reviewed the present status of the situation regarding the College

Headquarters, explaining that to date the Board had had only a committee headed by Dr Stengel who had reported informally upon preliminary possibilities. Now, with this resolution from the Board of Governors, one of the possible obstacles to this serious project had been removed. He asked for the judgment of the Board as to how best to proceed in the matter. He stated that he would make reference to it in his annual address at the Convocation and that the matter could be further mentioned at the Annual Business Meeting on March 5.

Dr O H Perry Pepper expressed the opinion that it would be proper to appoint a new committee to study the matter in detail, outlining it, get actual plans and actual estimates, but that that committee should not be empowered to proceed with the purchase of land or the erection of a building without further action by the Regents.

Chairman Miller explained that the committee that had been functioning thus far was appointed purely for a preliminary survey, that its work had probably been completed and that it might now be discharged with thanks.

Dr Stroud, Treasurer of the College, being asked for comments, expressed his approval of the idea of appointing a new committee, but suggested further that there should be included within the motion authorization for any financial outlay from the College funds as may be necessary for the services of an architect, etc.

Upon motion by Dr Biering, seconded by Dr Lee and regularly carried, it was

RESOLVED, that the temporary Committee on the College Headquarters be discharged with an expression of the deep thanks and appreciation of the Board of Regents for their general survey of the situation.

Chairman Miller pointed out that if it be the wish of the Board of Regents, the Board might proceed to definite plans for the acquisition of a new home and authorize the appointment of a definite committee for making concrete plans, and also to inform the Treasurer of such plans, because that might materially influence the disposition of funds that are now idle awaiting reinvestment.

In the discussion that followed, it was brought out that this might mean that the new committee would be authorized, if they felt wise, to employ an architect and to prepare definite plans. The committee would look into the particular proposition presented by the previous committee in Philadelphia and would also consider other suggestions concerning Washington, or any other city, but the Board of Governors were unanimous in expressing a preference for Philadelphia. The report of the new committee at the next meeting of the Board of Regents would have to be a very businesslike affair, not informal and not indefinite.

On motion by Dr Biering, seconded by Dr Bradley and regularly carried, it was

RESOLVED, that the incoming President shall appoint a Committee on College Headquarters which shall be authorized by the Board of Regents to proceed actively at once with detailed plans for the acquisition, or the construction, of a new College Headquarters, including the selection of a suitable site, the selection of the proper city, and, further, with authorization for preliminary expenditures for an architect, and with instructions to report to the Treasurer as to any financial arrangements entered into, so that proper funds may be available.

The report of this committee shall be presented to the Board of Regents as soon as feasible—a special meeting of the Board of Regents or the Executive Committee may be called if deemed advisable.

Dr Maurice C Pincoffs, Editor of the ANNALS OF INTERNAL MEDICINE, made a brief report to the effect that his work had been greatly aided by the temporary appointment of Dr Clough. Before another meeting he expressed the hope that that appointment may become permanent. He had been receiving a satisfactory number of manuscripts. The papers presented at the Annual Meeting remained the backbone of the publications in the ANNALS, and probably always will. He reported that unfortunately his office had gotten behind some weeks in getting out the journal recently. He expressed the assurance that the condition would be corrected.

In the absence of Dr Charles F Martin, Chairman of the Committee on Finance, Dr Roger I Lee presented the following report, which, upon motion, was accepted and filed

"Your Finance Committee beg to report a very satisfactory condition of the annual budget Detailed statement of this will be given by the Treasurer at the appropriate time

"They would draw attention to the fact that more than half of the gross income of \$72,000 is derived not from dues from members (which represents only \$31,000), but from the exhibits, subscriptions to the ANNALS, advertisements in the ANNALS and other minor sources of income

"Attention has been directed from time to time, to the substantial annual surplus of the organization in recent years On the other hand, your Committee would remind the Board of Regents that the income from the ANNALS and its advertisements is always a variable quantity according to the size of the ANNALS, the price of paper and printing, the cost of labor and the amount of advertising obtained,—that furthermore, an urgent need exists for more space in the executive offices, perhaps an increase in the personnel of the central office and an expense to be incurred through underwriting the Certification Board,—in all of which instances, increased demands will be made on the annual budget

"Your Committee approves the budget for 1936 as presented in the financial report of 1935

"Initiation Fees and Annual Dues In order to correct false impressions, they would remind the Regents, as well as the Fellows generally, that the initiation fee has been reduced to \$80, and that the annual dues of \$15 include the Journal

"They would recommend that an entertainment allowance for the President of \$200 be set aside in the budget to be drawn upon if, as and when required for special occasions

"It will be of interest to the Regents to know that the book value of securities today, in comparison with that of the original cost, will bring an enhancement of the values of securities and equities equivalent to approximately \$7,000

"The Finance Committee feels a responsibility with respect to your investments and suggests that a Trust Company, to be selected after due consideration by the President and Treasurer, be employed to act as agent to supervise the accounts of the College and advise with regard to investments, giving such suggestions to the Finance Committee as is dictated by their expert judgment They recommend that such a service be obtained from the best Trust Company in Philadelphia at a figure commensurate with the amount of capital involved—this service not to exceed, perhaps, \$300 per year

"Respectfully submitted,

" (Signed) C F MARTIN,

" *Chairman, Committee on Finance* "

Dr Stroud, Treasurer, explained that the handling of the investments is a heavy responsibility, and that it is difficult for the Committee on Finance to keep up with the rapidly changing ideas in investment principles College funds could be better and more safely invested if such counsel were available The responsibility for purchases and sales would still be with the Finance Committee, the investment counsel merely being an assistant agency in helping the Committee

Upon motion by Dr Pepper, seconded by Dr Lee, and regularly carried, it was

RESOLVED, that an appropriation of \$300.00 be added to the 1936 budget in accordance with the recommendation embodied in the last paragraph of the Finance Committee's report

Another item in the report requiring special consideration was the recommendation of the establishment of a fund of \$200.00 for the President's Entertainment Fund Dr Lee, in commenting upon the matter, pointed out that it is a very modest sum and the financial responsibilities that are indirectly put upon the President may in some instances be very large, and it seemed to the Finance Committee, despite the opposition of the President, that a moderate allowance was fitting for such an organization as the College to provide Dr Pepper, another member of the Committee, pointed out that the word "special" in the

report does not mean occasions other than those which may arise and always do arise at the Annual Meeting. In other words, it refers only to the usual entertainment incident to the Annual Meeting.

Upon motion by Dr. Piersol, seconded by Dr. Herrick, and regularly carried, it was

RESOLVED, that the sum of \$200.00 be appropriated for the year 1936-37, in accordance with the sixth paragraph of the Finance Committee's report.

Dr. William D. Stroud, Treasurer, distributed mimeographed copies of the annual report, which hereafter follow, and commented as follows:

"The annual report now in your hands explains the financial situation of the College. Mr. Loveland's report on page 1 shows that we have an Endowment Fund of \$58,281.72 and a General Fund of \$99,047.47, total assets of \$157,329.19. On our investments the total purchase price of our bonds is \$111,844.82, while an estimate of their sale value on February 28, 1936, taken from quoted prices, was \$116,130.15, an appreciation of more than \$4,000.00. The purchase price of our stock was \$14,811.00, which are now worth at current prices, \$17,902.00, therefore with an appreciation of over \$3,000.00. The total appreciation on bonds and stocks is therefore in excess of \$7,000.00."

Upon motion by Dr. Coeke, seconded by Dr. Lee, and regularly carried, it was

RESOLVED, that the report of the Treasurer be accepted and filed.

Chairman Miller pointed out that the budgets for the year 1936 had already been presented and passed upon by the Board of Regents at their meeting in Philadelphia, December 15, 1935, except for the two additions authorized at this meeting.

The report from the Committee on Fellowships and Awards, headed by Dr. David P. Barr as Chairman, was deferred for a later meeting.

Dr. Walter L. Biering, Chairman of the joint Committee on the Certification of Internists, reported that the Committee had held one meeting during this Session, and, in a tentative way, had added a few facts to what was reported previously. No special meeting of the Committee is planned at the Kansas City Session of the American Medical Association, except of those members who are required to bring the matter before the Section on the Practice of Medicine. It was contemplated that the first meeting of the American Board of Internal Medicine will be held during the first week in June for the purpose of working out further details (henceforth the joint Committee on the Certification of Internists will be referred to as the "American Board of Internal Medicine"). The Committee felt that one of its great problems will be the determination and selection of the Founders' Group.

Dr. O. H. Perry Pepper, a member of the Committee, expressed the suggestion that the Founders' Group might be built up very slowly. The determination of the Founders' Group must be based upon definite principles yet to be developed. Those selected must be men about whom there could be no question or criticism. Other opinions and plans were suggested by Dr. Meakins, also a member of the Committee.

On motion by Dr. Herrick, seconded by Dr. Pepper, and regularly carried, it was

RESOLVED, that the Board of Regents of the American College of Physicians approves of the plan of the Committee on the Certification of Internists as outlined for the American Board of Internal Medicine, and the Board of Regents authorizes its representatives on said Board to proceed, using their best judgment.

There was general discussion about any appropriations needed for the operation of the Committee before the next meeting of the Board of Regents. It had been pointed out that the Board of Regents had originally authorized the financing of this project to the limit of \$10,000.00, but that only \$1,000.00 specifically has been budgeted.

Upon motion by Dr. Pepper, seconded by Dr. Bradley, and regularly adopted it was

RESOLVED, that the Board of Regents shall appropriate a sum of \$4,000.00 additional, total \$5,000.00, on the 1936 budget to be made available, if necessary, for the American Board of Internal Medicine.

There was some discussion about a special meeting of the Board of Regents to be held for a final report from the Committee on College Headquarters and also from the American Board of Internal Medicine. The matter was left open, subject to the call of the President when such reports are ready and action necessary.

Dr John H Musser stated that he could not be present for the meeting of the Board of Regents on Friday, March 6, but wished to present to the Board an invitation for the Annual Session of 1938 to be held in New Orleans. An official invitation is being prepared by New Orleans, and will be sent to the Executive Secretary. He pointed out that just as the Twentieth Annual Session has been held in Detroit ten years following its previous meeting, the Twenty-second Annual Session, if held in New Orleans, would also be ten years after the previous meeting.

Chairman Miller asked Dr Musser if it would make any difference particularly to New Orleans whether the College came in 1938 or 1939, inasmuch as New York City also had been planning for sometime to present an invitation for 1938. Dr Musser replied that it will not, except for reasons of sentiment.

Dr William J Kerr at this point presented a memorial prepared by Dr C E Watts, Governor of the College for the State of Washington, on the death of Dr Frederick Epplen, for many years the College Governor for Washington.

On motion by Dr Kerr, seconded by Dr Biering, and regularly adopted, by rising vote, it was

RESOLVED, that the following tribute be recorded in the Minutes of the Board of Regents, that a copy be transmitted to Mrs Epplen, and that this memorial be published in the ANNALS OF INTERNAL MEDICINE.

IN TRIBUTE TO DR FREDERICK EPPLEN

"The Philadelphia Session last year was attended by Dr Frederick Epplen, who had been a member of the Board of Governors for many years. The question of his attending that last Session had been carefully considered and debated. He knew well that the trip to Philadelphia would cost him a large proportion of the myocardial compensation he possessed, but he felt sure that it would be the last opportunity of his lifetime. He elected to exchange most of his remaining strength and probably a part of the days left to him for the joy of association, the renewal of friendship, the revival of memories, in the College. Within the month he died, suddenly as he wished it, because he dreaded a lingering death.

"And thus passed one who was loved by all of us. He was not a prolific author, and yet he was well known the country over. By birth, training at home and abroad, and life long habit, his approach to medicine was intensely scientific rather than artful. He was rewarded with an unusually large practice for many years. The pressure of this professional work did not prevent him from maintaining his contacts and friendships in various organizations, especially in the College.

"The elevation of the level of medical practice in the Pacific Northwest was his constant desire. He gave much time and effort to the Pacific Northwest Medical Association, and the success of this adventure in postgraduate training stands as a tribute to him. A

firm believer in the County Medical Society as a disseminator of facts and ideas, he attended its meetings regularly, and he organized special societies in internal medicine, study clubs and discussion groups where needed

"As a means for the advancement of internal medicine and for improvement of all medicine, he believed thoroughly in the College of Physicians. His best efforts were given in its behalf. He acted as Governor for Washington for many years, and worked diligently in that capacity. He rarely failed to attend the Annual Sessions, and his friendships in the College were cherished as none other.

"During the last four years it was distressing to his friends to see him failing, and to have a cessation of activity in one who had been so energetic. Yet it was inspiring that his enthusiasm never waned, and his final effort to participate in the activities of the College was so characteristic of him and of what he held in highest esteem, that the memory of him will be with us always."

Adjournment

Attest E R LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF REGENTS

DETROIT, MICH

March 6, 1936

The third meeting of the Board of Regents during the Twentieth Annual Session was held on March 6, 1936, at the Book-Cadillac Hotel, Detroit, convening at 12 20 o'clock, with President Ernest B Bradley presiding, and with the following present: Ernest B Bradley, President, James H Means, President-Elect, David P Barr, Second Vice-President, William D Stroud, Treasurer, William Gerry Morgan, Secretary-General, James Alex Miller, Francis M Pottenger, Luther F Warren, William J Kerr, Roger I Lee, George Morris Piersol, G Gill Richards, Jonathan C Meakins, Maurice C Pineoffs, James D Bruce, and with Mr E R Loveland, Executive Secretary, acting as secretary of the meeting.

Upon motion, seconded and regularly carried, the reading of the Minutes of the previous meeting was dispensed with.

On motion by Dr J A Miller, seconded by Dr Stroud and regularly carried, it was

RESOLVED, that the President appoint a committee to revise and rewrite the present Fellowship Pledge of the College.

President Bradley appointed Dr James H Means, of Boston, a committee of one, to carry out the resolution.

President Bradley next brought up the matter of constitutional provisions for the endorsement of candidates either by a Governor, an Officer or a Regent. Although none of these may propose a candidate, some members of the Board of Governors have felt that it should be the policy of Officers and Regents to refrain from endorsing a candidate, so that all candidates may pass through their hands for investigation and final endorsement. Furthermore, President Bradley suggested that it might be more acceptable to the Committee on Credentials to have candidates endorsed by their respective Governors rather than Officers and Regents.

After general discussion, during which it was brought out that whether or not a proposal is endorsed by the Governor, it is always referred to the Governor by the Executive

Secretary, and the Governor given an opportunity to file his report before action by the Committee on Credentials, on motion by Dr James Alex Miller, seconded by Dr Means and regularly carried, it was

RESOLVED, that it is the sense of the Board of Regents that for the present at least it be considered desirable for no Officer or Regent to act as endorser of candidates, but rather that all proposals be referred to the Governor for the district from which the candidate comes

This resolution did not carry with it a recommendation of the changing of the By-Laws, which provide that an Officer or Regent may endorse a candidate as well as a Governor. The purpose of the resolution was merely to try out the plan of having all candidates endorsed officially by the Governor, so that in no case would the Governor be overlooked

The Executive Secretary, Mr Loveland, presented two communications from Dr James D Bruce, Governor for Michigan, recommending the reinstatement to Fellowship in the College of Dr Eva Finn and Dr William Clift, who had resigned five or six years ago. Their reinstatement was recommended by Dr Bruce in accordance with their desire to pay up past dues rather than being repropose as new cases

On motion by Dr Pottenger, seconded by Dr Lee and regularly carried, it was

RESOLVED, that Dr Eva Finn and Dr William Clift be reinstated as Fellows of the College subject to the payment of the dues from the time of their resignations to date

President Bradley at this time pointed out that the Constitution of the College permits specialists in other lines than Internal Medicine to become Fellows, such as roentgenologists, pathologists, pediatricians, neurologists, psychiatrists and others. There has been a growing tendency toward limitation of membership to those engaged in Internal Medicine. However, if such limitation shall be carried out, it will be plainly necessary to amend the Constitution and By-Laws. This could not affect those who are already members of the College, but would change the policy in connection with the election of new members in following the specialty of Internal Medicine

The Executive Secretary then presented the following communication and resolution from the Board of Governors, as adopted at their meeting on March 5

RESOLVED, that the Board of Governors suggest to the Board of Regents that each year the Executive Secretary send out appropriate questionnaires to obtain information as to the status and work that the members of the College have done during the preceding year, and that these records should be kept on file in the headquarters office

Later in the Minutes of the Board of Governors particular reference is made to Associates. The motion was intended to include all members of the College, but particularly Associates. The Board of Governors, in their discussion felt that there should be available up-to-date information about every member of the College, what he has done during the past year, his contributions, his new appointments, etc., they also felt that it would be a stimulus to Associates who are attempting to qualify for Fellowship for the College office to be following them up concerning these data each year

The Executive Secretary explained that this motion was initiated by some Governors of the College who had inquired for specific information concerning what certain physicians had done during the last two or three years. It not only was not available in the College, but could not be procured through the American Medical Association, or elsewhere. These men feel it desirable to have this information available in the College office about every man

Dr Bruce, speaking to the question, explained that a plan of this character had been employed at the University of Michigan with reference to postgraduate work for the past six years, and that he now has at his office in Ann Arbor the records of over three thousand of the Michigan State members concerning their attendance on various postgraduate activities, both within and out of the State. The plan has had a stimulating effect on the men. He recommended the idea as a very excellent one for the stimulation of Associates particularly

Dr James Alex Miller made inquiry as to the amount of work such a plan would entail in the Executive Offices, whether it would require additional clerical service, filing equipment, etc. The Executive Secretary replied that the present staff could take care of the work without excessive burden, but that additional space and files would be required. The volume of

material on file grows tremendously in an organization of this character. Mr. Loveland further explained that there is an individual folder for every Fellow and Associate of the College. The records, however, are often meagre for those members who have been in the College for many years, for in many instances no original application forms, or, for that matter, any other relevant records were received from the early executives of the College. However, records are fairly complete for all members from about 1920 forward, and wholly complete from 1926 forward.

On motion by Dr. Lee, seconded by Dr. Pincoffs and regularly carried, it was

RESOLVED, that a committee be appointed to draw up a plan for the sending out of blanks which will keep the College records up to date concerning the accomplishments of its Fellows and Associates, the committee to report back at the next meeting.

President Bradley subsequently appointed the following committee:

James D. Bruce, Chairman

Jonathan C. Meakins

Maurice C. Pincoffs

In the discussion, it was brought out that these blanks are intended primarily to keep the College records up to date as to the accomplishments of our Fellows and Associates, that the first records at least shall be complete for a man's entire history, and that the annual form sent out thereafter shall be intended merely to supplement the original record.

Dr. James Alex. Miller proposed that inasmuch as the formation of the American Board of Internal Medicine and the activities of other committees, such as that of the Committee on Credentials, will affect the constitutional requirements for admission to the College, that the Committee on Constitution and By-Laws review and, perhaps, present proper amendments at the next meeting of the Board of Regents. He pointed out that our Constitution says that Fellows shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine or in an allied specialty. Perhaps the last clause should be deleted.

President Bradley pointed out that in the appointment of new committees due consideration will be given to overlapping certain appointments, so that the Committee on Constitution and By-Laws will have a better appreciation of any amendments that may be necessary.

On motion by Dr. J. A. Miller, seconded by Dr. Richards and regularly carried, it was

RESOLVED, that there be referred to the Committee on Constitution and By-Laws a request for a report and suggested changes in the Constitution and By-Laws to meet the new demands of the College standards for qualification for Internal Medicine.

Dr. Miller's motion had in mind the preparation of such amendments as may be made necessary by the further restriction of the College membership to internists, as may be occasioned particularly by the operation of the new American Board of Internal Medicine.

The next matter of business was the election of a Secretary-General and of a Treasurer for 1936-37.

Dr. George Morris Piersol nominated Dr. William Gerry Morgan for reelection, Dr. Luther F. Warren seconded the nomination.

President Bradley called for other nominations, of which there were none.

Dr. William Gerry Morgan was unanimously elected Secretary-General for the year 1936-37.

Dr. George Morris Piersol nominated Dr. William D. Stroud for reelection as Treasurer, Dr. J. A. Miller seconded the nomination.

By motion seconded and regularly carried, nominations for Treasurer were closed.

Dr. William D. Stroud was unanimously elected Treasurer for the year 1936-37.

On inquiry by a member of the Board, it was disclosed that the Treasurer is bonded in the amount of \$50,000.00.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported for that Committee, reading a letter from Dr. John P. Peters concerning Dr. Michael J. Lepore, who is the American College of Physicians Research Fellow at Yale University for

1935-36 Dr Peters' letter revealed that he considers the granting of these fellowships as the most worthy thing the College carries on Dr Lepore's work was reported on in detail, with most favorable comment

Dr Barr then reported that the Committee recommends to the Board of Regents the appointment of Myron Prinzmetal as Research Fellow for 1936-37 Dr Prinzmetal was graduated in 1932 from the University of California His record in school was extraordinary He worked in the Department of Pharmacology, the Department of Pathology and the Department of Medicine as a student and in each of these did investigative work of high order Two years ago he was appointed National Research Fellow, letters from his former teachers were of the most enthusiastic kind Dr Barr stated that his Committee believed that Dr Prinzmetal was considered the outstanding graduate not only of his year, but, perhaps, for five years He later went to the Barnes Hospital, St Louis, for a year as Assistant Resident, where he took part in some of the researches conducted by Dr Kountz He then went to the Boston City Hospital under Dr Soma Weiss As a result of the work with Dr Weiss, he published a paper, "The Nature of the Peripheral Resistance to Arterial Hypertension, with Special Reference to the Vasomotor System" Dr Barr passed a reprint of this publication around for examination by the Board Dr Prinzmetal had published about twenty-four papers even preceding the one in question, most of his publications in association with men from the various schools in which he had worked

Dr Barr stated that he was familiar with most of Dr Prinzmetal's publications, and stated that he (Dr Prinzmetal) had contributed much more than the ordinary assistant does contribute to researches with older men The Committee is informed Dr Prinzmetal wishes to pursue further work with Sir Thomas Lewis in London, especially to continue research on hypertension The Committee, therefore, recommended to the Board of Regents Dr Prinzmetal's selection for the Research Fellowship for the year 1936-37

Upon motion by Dr Lee, seconded by Dr Meakins and regularly carried, it was

RESOLVED, that Dr Myron Prinzmetal be awarded the Research Fellowship of the American College of Physicians, amounting to \$150.00 per month for twelve months, beginning July 1, 1936

Dr Stroud inquired whether in view of the fact that some felt there should be additional fellowships, Dr Michael J Lepore now working at Yale University and whose fellowship expires in June might not be considered for an additional year

Dr Barr, for the Committee on Fellowships and Awards, reported that Dr Lepore had not requested a continuation of his fellowship, and expressed the belief that Dr Lepore might be provided for directly in the budget at Yale Dr Barr expressed a doubt as to there being any necessity the present year to consider the extension of his fellowship He said further that in appointing a Fellow the College assumes at least a great interest in that man and a certain degree of responsibility for seeing that he has the opportunity to develop from this grant, and when and if the College funds permit the extension of fellowships in this form or in other forms, the matter should be actively considered by the Regents

Dr Barr was informally authorized by President Bradley to write Dr Peters, thanking him for his report on the work of Dr Michael J Lepore, and to convey to Dr Peters the very great interest of the College in Dr Lepore's work, also to find out, without in any way committing the College, what provision is being made for Dr Lepore next year

Dr Richards inquired from Dr Barr whether in his opinion the College would accomplish more good by extending a fellowship for two years, or to award separate fellowships to different men

Dr Barr's reply was that he feels that one year is preferable, because each one of these fellowships is, to a degree, a gamble, it cannot be determined how the one selected will succeed, in one year he has an opportunity of showing how good he is, if he is very good, the College, perhaps, should consider him for a second year

Dr James Alex Miller "Mr President, in this connection, following up the line on which I spoke at the General Business Meeting yesterday, it does seem to me that we ought to be thinking over, in connection with our plans for a new home, also the question of a

program for possibilities of using surplus funds for the advancement of Internal Medicine. This granting of Fellowships would be one method, there may be others. It seems to me that it would be very helpful if, in addition to your specific committee that has already been authorized for the consideration of specific plans and estimates for our new home, we had at the same meeting a report from another committee that might consider other possibilities for a program of funds, with some estimate of what that would involve, which would help us to determine another thing, that is, this question as to in what way, if any, we should reduce the financial obligations of the new Fellows. It seems to me that it might help in this whole matter if we at this meeting authorize the appointment of another committee to report at the same time that the House Committee does, in connection with the possibility of a future program for the use of available funds of the College for the promotion of Internal Medicine, leaving it open to more fellowships or something else.

"Dr. Pincoffs made the suggestion of some sort of revolving fund and some of us have been discussing a revolving fund that might be given to young men, that would be turned back. If it was similar to other revolving funds, it might be of great value to this organization. That money would very likely come back, come back to us with interest.

"In other words, there is quite a field there and I think that while we are considering this new home, the Fellowship of the College would be very much interested to know how much we have been considering other possible programs for the use of our money and, if they could consider them altogether, it would seem to me it would be very helpful."

In the discussion that followed, Dr. Miller indicated that this additional program would not be limited to fellowships and awards alone, but that there should be some committee to take up a composite program that would include everything that the College might consider.

Dr. Kerr said that as soon as the American Board of Internal Medicine is established and begins to function, queries will probably begin to come in as to facilities for training as internists in this country. The College should be prepared to furnish such information about these facilities both in this country and abroad. He suggested that the College might definitely consider the investment of some of its funds in assisting young men who cannot afford to continue their training as they should. But, the College should be well informed and be well prepared, through a survey, before launching on any particular project.

On motion by Dr. Pincoffs, seconded by Dr. Barr and regularly carried, the following resolution was adopted:

RESOLVED, that a Committee on Future Policy for the development of Internal Medicine be appointed by the President for the purpose of considering a program of possibilities for using surplus funds for the advancement of Internal Medicine. This committee shall take under consideration all matters outside of that of the College Headquarters, such as fellowships, awards, postgraduate education, initiation fees of new Fellows, revolving funds for the aid of research, etc.

President Bradley subsequently appointed the following Committee:

James Alex. Miller, *Chairman*
Walter L. Biering
Roger I. Lee
Maurice C. Pincoffs
Francis M. Pottenger

The following Executive Committee of the Board of Regents was elected for the year 1936-37:

Ernest B. Bradley, *Chairman*
James H. Means
William Gerry Morgan
William D. Stroud
Walter L. Biering
Roger I. Lee
James Alex. Miller
Maurice C. Pincoffs
Francis M. Pottenger

President Bradley proceeded to the appointment of committees in accordance with the Constitution and By-Laws or special regulations previously adopted by resolution by the Board of Regents (asterisk indicates new appointment, \ indicates reappointment)

Committee on Advertisements and Commercial Exhibits

\E J G Beardsley, *Chairman*
 \George Morris Piersol
 \William D Stroud

* * * * *

Committee on Annals of Internal Medicine

\James H Means, *Chairman* (1939)
 David P Barr (1938)
 *Egerton L Crispin (1937—taking the place of O H
 Perry Pepper, resigned)

* * * * *

Committee on Fellowships and Awards

xDavid P Barr, *Chairman*
 *Jonathan C Meakins
 \James H Means
 \William J Kerr
 *Hugh J Morgan

* * * * *

Consulting Committee on Annual Sessions

Ernest B Bradley, *Chairman*
 David P Barr
 James Alex Miller
 Jonathan C Meakins
 Alfred Stengel

The Consulting Committee on Annual Sessions is automatic in its appointments, being made up of the President and General Chairman of the current and last two sessions

Committee on Constitution and By-Laws

Jonathan C Meakins, *Chairman* (1938)
 Alfred Stengel (1937)
 *James B Herrick (1939)

* * * * *

Committee on Credentials

Representing the Board of Regents

*Sydney R Miller, *Chairman* (1939)
 Luther F Warren (1938)
 George Morris Piersol (1937)

(The three representatives appointed by the Board of Governors included)

William B Breed (1937)
 Charles H Cocke (1938)
 *J Owsley Mamer (1939)

* * * * *

Committee on Finance

*James Alex Miller, *Chairman* (1939)
 O H Perry Pepper (1938)
 Roger I Lee (1937)

* * * * *

Committee on Nominations

George Morris Piersol, *Chairman* (from the Board of Regents)
 James D Bruce (from the Board of Regents)
 William B Breed (from the Board of Governors)
 Charles T Stone (from the Board of Governors)
 Charles F Martin (Member-at-Large)

* * * * *

Committee on Public Relations

*James E Paullm, *Chairman* (1939)
 *Robert A Cooke (1940)
 Walter L Bierring (1937)
 James F Churchill (1938)

Ex Officio

Ernest B Bradley

Committee on Certification of Internists
 (American Board of Internal Medicine)

This Committee remains as previously appointed

Walter L Bierring, *Chairman* (A M A)
 Reginald Fitz (A M A)
 Ernest E Irons (A M A)
 James H Means (A M A)
 David P Barr (A C P)
 Jonathan C Meakins (A C P)
 William S Middleton (A C P)
 O H Perry Pepper (A C P)
 G Gill Richards (A C P)

* * * * *

Committee on College Headquarters

Roger I Lee, *Chairman*
 O H Perry Pepper
 William D Stroud
 James Alex Miller
 David P Barr

The Executive Secretary then presented invitations for the 1937 Annual Session from the Cities of Columbus, Buffalo, Cleveland, Toledo, Memphis and St Louis, including one for 1938 from New Orleans. The two most complete invitations were from Memphis and St Louis, and were read in detail. They contained official invitations from all the medical organizations, the medical school, civic bodies, hotels, Chamber of Commerce, the Governor for the State, the local Regent and Fellows, and others.

On motion by Dr J A Miller, seconded by Dr Piersol and regularly carried it was RESOLVED, that the Twenty-First Annual Session of the American College of Physicians be held in St Louis during 1937

On motion by Dr Barr, seconded by Dr Richards and regularly carried, it was RESOLVED, that the date of the meeting shall be during the third week of April, namely, April 19-23, 1937

Dr James Alex Miller reported that he has been discussing with keymen in New York City the possibility of the College coming to New York in 1938, and expressed the opinion that there will undoubtedly be a complete invitation laid before the College for the 1938 Session

On motion by Dr Meakins, seconded by Dr J A Miller and regularly carried, it was RESOLVED, that Dr David P Barr shall act as the General Chairman of the 1937 Session in St Louis

Dr G Gill Richards inquired why the Daily Bulletin had been discontinued at the 1936 Session, saying that several inquiries had come to him from members in attendance who missed the Bulletin

The Executive Secretary, Mr Loveland, reported that the Daily Bulletin had never been officially established by the Board of Regents, but had been published by him primarily for the exhibitors. It had entailed a tremendous amount of work because each issue had to be published over night with a great deal of work in preparing copy, proof reading, etc. Furthermore, its publication had entailed an expense of from three to four hundred dollars. He said that the bulletin was not serving any valuable purpose so far as exhibitors were concerned. The daily registration of attendants at the Session is of some value, but will be furnished to exhibitors after the meeting. He reported that the Editor of the ANNALS had preferred not to act as editor of the Daily Bulletin, and it had been discontinued at the Detroit meeting purely because of the burden of work entailed by its publication

President Bradley asked for the opinion of the Board of Regents, saying that if they felt it worth while, the Executive Secretary would be glad to publish it

On motion by Dr Piersol, seconded by Dr J A Miller and regularly carried, it was RESOLVED, that the publication of the Daily Bulletin at the Annual Sessions be discontinued because of the amount of work and the expense attached

President Bradley, speaking about the present Session and the one for 1937, informed the Board of Regents that he would like to have a free expression of recommendations and suggestions for the program next year. He stated he had talked with many of the members of the College about the program of the Detroit Session, and without a dissenting voice, the opinions had been that the program was excellently arranged. Sometimes addresses were considered too numerous for the time available at former meetings, but there had been no such criticism at the current meeting. He had also talked with the exhibitors, who expressed their appreciation of the forty-five minute intermissions in the General Sessions. Some of them felt that the program ran too late in the afternoon, and expressed the desire to have a little more time open for the inspection of exhibits. Exhibitors had expressed some question as to the desirability of his suggestion that the intermissions might be shorter with earlier closing in the afternoon. President Bradley stated that he felt it should be announced by every presiding officer on the afternoon session before intermission that this time is given attendants solely for their visit to and inspection of the exhibits, and suggested that this announcement be placed on the afternoon agenda in the future

Dr David P Barr inquired if it were the feeling of the Board that it is necessary to have a considerable competition of clinical programs or a greater number of clinical programs each morning. He suggested the possibility that at St Louis he might be able to arrange two, or at the most three, programs of high excellence, with halls sufficiently large to accommodate the people who wish to come, and inquired whether the Board felt that at the same time there should be a larger number of programs in other places. At some of the Sessions there are about twenty different clinics going on simultaneously

President Bradley, referring to the didactic morning lectures at the Philadelphia Session, reported that the chairman of the clinics, Dr Pepper, had found that they were rather popular among some of the men who did not wish to go further and join to various hospitals and laboratories for clinics. It was offered as a suggestion for consideration at the St Louis meeting again. President Bradley said that he saw no particular reason why men should be sent to hospitals unless patients were to be shown and real clinics given.

Dr Stroud inquired whether by doing this there might not be some danger of curtailing the attendance at the various clinics.

Dr Lee expressed the opinion that it is merely a question of competing against one's self in either event. He personally had a strong feeling that the mornings are clinical sessions, but that there has been a strong drift against the clinical session in the hospital, yet these clinics are the real keynotes of the meetings and the members ought to be encouraged to go to the hospitals, otherwise the actual purpose of the College is defeated. He said further that the only criticisms he had heard were that the standard of both the clinics and the lectures should be raised, getting them out of the district medical society level to which they have drifted and getting them on the level of internists.

Dr Meakins said that he had been very much impressed for quite a few years with the fact that the morning sessions, while they are supposed to be clinical, seldom provide patients. There have been lantern slides and x-rays. At his clinic that morning he had been the only one who had presented patients. The other patients were there, but were not used, they were left in the background and the speakers talked from slides, etc. The previous morning he had been at a dermatological clinic, and it had been most illuminating because they had something one can see. If the patient is not going to be used, if it is not going to be a real clinical program, why should the members of the College be put to the bother and trouble of going off to a distant hospital several miles away? Why should such presentations not be given at the headquarters?

Dr Means stated that he heartily endorsed the sentiments of Dr Meakins. He thought it very necessary to get back to the presentation of patients.

Dr Pincoffs stated that he thought there are other features that could be developed that have been present at some of our meetings, one of which is the mornings at home for people in the laboratories. He referred especially to the Thorndike Laboratory in Boston, where this idea was well carried out. It was also carried out by a number of men in Philadelphia. Many men visiting those laboratories spoke highly of that feature.

Dr Meakins further pointed out that if the College is to have real clinics it cannot have them in a place that seats two hundred people, because they can't see anything. Real clinics must be conducted in smaller groups.

President Bradley, in discussing the date of the next meeting of the Board of Regents, suggested that it might be necessary to call a meeting during the summer or the very early autumn, in order to receive reports from the Committee on the College Headquarters, the American Board of Internal Medicine and the Committee on Future Policy for the Development of Internal Medicine.

Adjournment

Attest E. R. LOVELAND,
Executive Secretary

ANNALS OF INTERNAL MEDICINE

AUTHOR INDEX

Volume 9, 1935-1936

- ABRAMSON, D I, G H ROBERTS and—
Ventricular Complexes of the Bundle-Branch Block Type Associated with Short P-R Intervals 983
- ABRAMSON, D I, J WEINSTEIN and—
Localization of the Site of Experimental Premature Contractions and Bundle Branch Lesions by Means of Multiphase Chest Leads 1187
- ADAMS, M, M H POWER and W M BOOTHBY Chemical Studies in Myasthenia Gravis 823
- ADAMS, M, M H POWER and W M BOOTHBY Metabolism Studies in Myasthenia Gravis before and during the Administration of Glycine 1330
- ALEXANDER, F and W HEALY Roots of Crime Psychoanalytic Studies *Rev* 354
- ALLEN, E V and R K GHORMLEY Lymphedema of the Extremities Etiology, Classification and Treatment, Report of 300 Cases 516
- ALTSHULER, S S and S E GOULD Diabetes Refractory to Insulin *Case Rep* 1595
- ANDERSON, J P Neurocirculatory Asthenia Report of a Case Treated by Adrenal Denervation *Case Rep* 1255
- ANDRUS, E C and D McEACHERN Studies on the Increased Metabolism in Hyperthyroidism 579
- ANSPACH, B M Gynecology *Rev* 1606
- ASCHER, M S, G L WALDBOTT and—
The Role of Accidental Puncture of Veins in the Production of Allergic Shock 1232
- AYKROYD, W R Three Philosophers (Lavoisier, Priestley and Cavendish) *Rev* 1440
- BAKER, R L, E E OSOON, M F GOURLEY and— Diagnosis of Dissecting Aneurysm of the Aorta 1398
- BAKER T W, N W BARKER and—
Proliferative Intimitis of Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis and Recurring Necrotic Ulcers of the Skin *Case Rep* 1134
- BAKST, H J, J A FOLEY and M E LAMB Gonorrheal Septicemia and Erythema Nodosum *Case Rep* 790
- BALFOUR, D C, ELSTERMAN, G B and— The Stomach and Duodenum *Rev* 1755
- BARACH, A L The Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larynx and Trachea 739
- BARACH, A L, D W RICHARDS and W B PARSONS Oxygen Treatment and Thyroid Ablation in the Treatment of Heart Disease 1513
- BARBORKA, C J Treatment by Diet *Rev* 97
- BARGEN, J A, H C OCHSNER and—
Diverticulosis of the Large Intestine, An Evaluation of Historical and Personal Observations 282
- BARKER, N W and T W BAKER Proliferative Intimitis of Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis, and Recurring Necrotic Ulcers of the Skin *Case Rep* 1134
- BAUER, W, P S HENCH, A A FLETCHER, D GHRIST, F HALL and T P WHITE The Present Status of the Problem of "Rheumatism" and Arthritis, Review of American and English Literature for 1934 883
- BEARDWOOD, J T, JR, and H T KELLY Simplified Diabetic Management *Rev* 97
- BECK, E C, J G FOWLER, E C KOENIG and B D BOWEN Vascular Disease in the Obese Diabetic and in Non-Diabetics, A Discussion of Arteriosclerosis as a Cause of Diabetes 662

- BERNHARD, A, H A RAISKY,—and
G L ROHDENBURG Studies in Hy-
pertension, A Proposed Classifica-
tion of Hypertension Based upon the
Nitrogen Distribution of the Serum
Proteins 1091
- BITZER, E W Observations on the
Effect of Sudden Changes in Ar-
terial Tension in Angina Pectoris 1120
- BLECH, G M and C LANCHE Medical
Tactics and Logistics *Rev* 1440
- BIOTNER, H Excessive Smoking as a
Possible Precipitating Factor in Dia-
betic Gangrene, with a Case Report
Case Rep 987
- BLUMER, G and A I SULLIVAN The
Practitioner's Library of Medicine
and Surgery Vol VIII Thera-
peutics *Rev* 210
- BLUMER, G (Supervising Editor), J
C FOX, JR and C C FRY (Associ-
ate Editors) The Practitioner's Li-
brary of Medicine and Surgery
Volume IX Neurology and Psychi-
atry *Rev* 1268
- BOARDMAN, W W Dimetrophenol and
Rapidly Developing Cataracts *Case
Rep* 195
- BOLLMAN, J L and F C MANN
Alterations in Hepatic Function Pro-
duced by Experimental Hepatic Le-
sions 617
- BOOTHBY, W M Myasthenia Gravis 143
- BOOTHBY, W M, M ADAMS, M H
POWER and— Chemical Studies in
Myasthenia Gravis 823
- BOOTHBY, W M, M ADAMS, M H
POWER and— Metabolism Studies
in Myasthenia Gravis before and dur-
ing the Administration of Glycine 1330
- BOWEN, B D, E C BECK, J G
FOWLER, E C KOENIG and— Vas-
cular Disease in the Obese Diabetic,
and in Non-Diabetics, A Discussion
of Arteriosclerosis as a Cause of
Diabetes 662
- BRAIN, W R Diseases of the Nerv-
ous System *Rev* 641
- BRAY, G W Recent Advances in Al-
lergy *Rev* 808
- BRIDGES, M A Dietetics for the Clin-
ician *Rev* 210
- BRITTON, C J C, L E H WHITBY
and— Disorders of the Blood
Rev 1441
- BROWN, G E Surgical Procedures in
Essential Hypertension *Edit* 488
- BROWN, P W and J DE J PERMERTON
Solitary Ulcer of the Ileum and
Ulcer of Meckel's Diverticulum 1684
- BURBANK, B and E ROTHSTEIN
Artificial Pneumothorax in the
Treatment of Lobar Pneumonia 376
- BURCH, H A, B R KIRKLIN and—
Incidence and Significance of the
Roentgenologic Niche in Duodenal
Ulcer 436
- CABOT, R C Physical Diagnosis
Rev 1440
- CALLOMON, V B and J UNGAR
Treatment of Pneumonia with Serum
Containing Type-Specific, Hetero-
phile, and Neutralizing Antibodies 1664
- CAMFRON, D E Objective and Ex-
perimental Psychiatry *Rev* 809
- CANNON, A and E D T HAYES
The Principles and Practice of Neu-
rology *Rev* 96
- CANNON, W B The Role of Emotion
in Disease 1453
- CASAMAJOR, L Some Factors in the
Etiology of the Psychoneuroses 1677
- CHILLINGWORTH, F P, J C HEALY,
M H SWIFT and— Effect of Vi-
bratory Stimulation on the Neutro-
philic Index 123
- CLARK, E R Growth and Develop-
ment of Function in Blood Vessels
and Lymphatics 1043
- CLARK, J H, L G ROWNTREE,—A
STEINBERG, A M HANSON, N H
LINHORN and W A SHANNON
Further Studies on the Thymus and
Pineal Glands 359
- CLERF, L H The Present Status of
Bronchoscopy in Bronchial Asthma 1050
- COHEN, A, J GOLDMAN and— Ab-
dominal Distention in Lobar Pneu-
monia 1222
- COLLIP, J B Recent Studies on Anti-
Hormones 150
- COOKE, W C The Beneficial Effect
of the Development of an Abnormal
Rhythm with Slow Ventricular Rate
in Circulatory Failure *Case Rep* 1143

- CORR, P Intensive Liver Therapy in Sprue 1182
- COWAN, J and W I RITCHIE Diseases of the Heart *Rev* 1607
- CRAIG, C F Amebiasis and Amebic Dysentery *Rev* 492
- CRAWFORD, P M, R M HARDAWAY and— Pulmonary Torulosis *Case Rep* 334
- CRIMM, P D and J W STRAYER Phosphatase Content of Human Serum in Pulmonary Tuberculosis Following the Administration of Vitamin D 1393
- DAVIES, J A V, C F MCKHANN, A A GREEN, L E ECKLES and— Immunological Applications of Placental Extracts, Effectiveness by Oral Administration 388
- DELLINGER, S C, E G WAKEFIELD and— A Report of Identical Albino Twins of Negro Parents *Case Rep* 1149
- DELLINGER, S C, E G WAKEFIELD and— Diet of the Bluff Dwellers of the Ozark Mountains and Its Skeletal Effects 1412
- DEWEY, E Behavior Development in Infants, a Survey of the Literature on Pre-Natal and Post-Natal Activity, 1920-1934 *Rev* 1158
- DIMMITT, P S Clinical Laboratory Methods *Rev* 1606
- DOUGLAS, A H, C SHOOKHOFF,—and M A RABINOWITZ Sedimentation Time in Acute Cardiac Infarction 1101
- DUNCAN, G G Diabetes Mellitus and Obesity *Rev* 641
- DUNHAM, K and J H SKAILEM Basic Points in Roentgen-Ray Studies of Lung Anatomy and Pathology 555
- DYER, R E, W M CLARK, R G HARRISON, E A DOISY, E A GRAHAM, G L STREETER, T M RIVERS and D W BRONK The Harvey Lectures, 1933-1934, Series XXIX *Rev* 97
- ECKLES, L E and J A V DAVIES, C F MCKHANN, A A GREEN,— Immunological Applications of Placental Extracts, Effectiveness by Oral Administration 388
- EINHORN, N H and W A SHANNON, L G ROWNTREE, J H CLARK, A STINBERG, A M HANSON,— Further Studies on the Thymus and Prenal Glands 359
- ELMER, W P and W D ROSE Physical Diagnosis *Rev* 492
- EMERSON, C P The Nervous Patient *Rev* 353
- EMERY, E S, JR, P H WOSIKA and— The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice of Patients If the Amount of Alkali Is Not Varied 1070
- EMERY, E S, JR, P H WOSIKA and — The Value of a Mixture of Powdered Milk and Alkali for Neutralizing the Gastric Acidity of Patients with Peptic Ulcer 1078
- EPSTEIN, N N, F KELLOGG,—and W J KERR Hepatic Complications in the Treatment of Syphilis II Incidence of Hepatic Disease in Patients with Untreated Syphilis and during Their Subsequent Treatment 1561
- ESCAMILLA, R F, H LISSER and H C SHEPARDSON Internal Myxedema, Report of a Case Showing Ascites, Cardiac, Intestinal and Bladder Atony, Menorrhagia, Secondary Anemia and Associated Carotinemia 297
- EUSTERNAN, G B and D C BALFOUR The Stomach and Duodenum *Rev* 1755
- EVANS, W A Long-Standing Cases of Auricular Fibrillation with Organic Heart Disease, Some Clinical Considerations 1171
- FAUST, D B Pancreatic Lithiasis *Case Rep* 625
- FELDMAN, L The Initial Ventricular Complex of the Electrocardiogram in Coronary Thrombosis 1714
- FELDMAN, L, I M TRACE and M I KAPLAN "Eventration" of the Right Diaphragm Report of a Case with Review of the Literature, Chiefly from the Standpoint of Etiology and Diagnosis 62
- FERNAN-NUÑEZ, M Blackwater Fever A Clinical Review of Fifty-Two Cases 1203
- FETTER, F, T G SCHNABFL and—

- Fever Therapy in Gonorrheal Arthritis and Chorea 398
 FLETCHER, A A, D GHRIST, F HALL and T P WHITE, P S HINCH, W BAUER,— The Present Status of the Problem of "Rheumatism" and Arthritis, Review of American and English Literature for 1934 883
 FINN, I W, R S FINN and Z M FINN A Study of Nine Cases of Bronchomoniasis 42
 FINN, L B Acute Lymphatic Leukemia in a Child of Four Years with a Severe Granulopenic Phase Preceding a Remission 458
 FOLLY, J A, H J BAKST,—and M E LAMB Gonorrheal Septicemia and Erythema Nodosum *Case Rep* 790
 FOUCAR, F H Acute Fulminating Meningococcus Infection, with Bilateral Capillary Hemorrhage of the Adrenals as the Most Striking Gross Pathologic Lesion *Case Rep* 1736
 FOWLER, J G, E C KOENIG and B D BOWEN, E C BECK,— Vascular Disease in the Obese Diabetic, and in Non-Diabetics, A Discussion of Arteriosclerosis as a Cause of Diabetes 662
 FOWLER, W M Thrombopenic Purpura, An Analysis of 160 Cases 1475
 FOX, J C, JR, and C C FRY (Associate Editors), G BLUMER (Supervising Editor) The Practitioner's Library of Medicine and Surgery Volume IX Neurology and Psychiatry *Rev* 1268
 FREEMAN, W Personality and the Endocrines, A Study Based upon 1400 Quantitative Necropsies 444
 FRY, C C, J C FOX, JR and—(Associate Editors), G BLUMER (Supervising Editor) The Practitioner's Library of Medicine and Surgery Volume IX Neurology and Psychiatry *Rev* 1268
 GAMBLE, C J, I STARR, JR and— Cardiac Output in Common Clinical Conditions, and the Diagnosis of Myocardial Insufficiency by Cardiac Output Methods 569
 GAUSS, H The Interrelationship of Gastrointestinal and Renal Disease 1373
 GIGER, A J, P W PRIU and— Symptomatic Psychoses in Pernicious Anemia 766
 GINTZKOW, C J, J S SIMMONS and—(Editors) Laboratory Methods of the United States Army *Rev* 1268
 GINSBERG-COHEN, J, H SHAY and— A Comparison of the Effectiveness of Glutamic Acid Hydrochloride and Dilute Hydrochloric Acid as the Replacement Therapy in Anacidity Measured by Fractional Gastric Acid Titration and Hydrogen-Ion Concentration Curves 1628
 GORMLEY, R K, L V ALLEN and— Lymphedema of the Extremities Etiology, Classification and Treatment, Report of 300 Cases 516
 GHRIST, D, F HALL and T P WHITE, P S HINCH, W BAUER, A A FLETCHER,— The Present Status of the Problem of "Rheumatism" and Arthritis, Review of American and English Literature for 1934 883
 GOLDMAN, J and A COHEN Abdominal Distention in Lobar Pneumonia 1222
 GOLDSMITH, G A The Effectiveness of Acetyl-B-Methylcholine Given by Mouth as a Vasodilating Agent 1196
 GOLDZIEHER, M A Practical Endocrinology Symptoms and Treatment *Rev* 1160
 GOODMAN, N G Benjamin Rush, Physician and Citizen *Rev* 1606
 GOODWIN, G M Russell A Hibbs *Rev* 810
 GORDON, A Late Recrudescence in Encephalitis Lethargica with Succession of New Manifestations at Intervals of Years, the Problem of Prognosis 1725
 GORDON, M B and M J WALLFIELD Toxic Reaction to Alpha-Dinitro-Ortho-Cresol *Case Rep* 198
 GOULD, S E, S S ALTSHULER and— Diabetes Refractory to Insulin *Case Rep* 1595
 GOURLEY, M F, E E OSGOOD,—and R L BAKER Diagnosis of Dissecting Aneurysm of the Aorta 1398
 GRADWOHL, R B H Clinical Laboratory Medicine and Diagnosis *Rev* 490
 GRIFIN, A A, C F MCKHANN,—L

- E ECKHFS and J A V DAVIS
Immunological Applications of Placental Extracts, Effectiveness by Oral Administration 388
- GREENBAUM, S S, H PRINZ and—
Diseases of the Mouth and Their Treatment *Rev* 811
- HADDEN, S B Neurological Symptoms in Posthemorrhagic Secondary Anemia 1572
- HALL, F and T P WHITE, P S HENCH, W BAUER, A A FLETCHER D GHRIST,— The Present Status of the Problem of "Rheumatism" and Arthritis, Review of American and English Literature for 1934 883
- HAMILTON, J R The Practical Use of Hobbies in the Practice of Medicine 1129
- HANRAHAN, E M Thrombopenic Purpura *Edit* 352
- HANSON, A M, N H EINHORN and W A SHANNON, L G ROWNTRFE J H CLARK, A STEINBERG,— Further Studies on the Thymus and Pineal Glands 359
- HARDWAY, R M and P M CRAWFORD Pulmonary Torulosis *Case Rep* 334
- HARNES, A R Clinical Management of Syphilis *Rev* 353
- HARTUNG, E F and O STEINBROCKER Gastric Acidity in Chronic Arthritis 252
- HAYES, E D T, A CANNON and— The Principles and Practice of Neurology *Rev* 96
- HAYES, J N Oleothorax Clinical and Experimental 779
- HEFALY, J C, M H SWEET and F P CHILLINGWORTH Effect of Vibratory Stimulation on the Neutrophilic Index 123
- HEFALY, W, F ALEXANDER and— Roots of Crime Psychoanalytic Studies *Rev* 354
- HEFFRON, R, F T LORD and— Lobar Pneumonia and Serum Therapy *Rev* 1756
- HENCH, P S, W BAUER, A A FLETCHER, D GHRIST, F HALL and T P WHITE The Present Status of the Problem of "Rheumatism" and Arthritis, Review of American and English Literature for 1934 883
- HENRY, G W Essentials of Psychopathology *Rev* 1269
- HERRMANN, G R Synopsis of Diseases of the Heart and Arteries *Rev* 1754
- HERTZLER, A E Diseases of the Thyroid Gland *Rev* 809
- HITZROT, L H, E M LANDIS and— Treatment of Peripheral Vascular Disease by Means of Suction and Pressure 264
- HODGES, F J The Medical and Economic Advantages of a Roentgen-Ray Chest Survey of All Hospital Admissions 1639
- HODGSON, V H Public Health Nuisance in Industry *Rev* 354
- HOLMES M E Fatal Diabetic Coma with Acute Renal Failure 426
- HUDDESON, I F Brucella Infections in Animals and Man Methods of Laboratory Diagnosis *Rev* 212
- HULL, E and L A MONTE The Treatment of Acute Mercuric Chloride Poisoning 54
- HULL, H L A Study of 118 Readmissions to Oakhurst Sanatorium of Grays Harbor County Washington 134
- HUNT H M, L M HURATHAL and— Clinical Relationships of Blood Cholesterol with a Summary of Our Present Knowledge of Cholesterol Metabolism 717
- HURATHAL L M and H M HUNT Clinical Relationships of Blood Cholesterol with a Summary of Our Present Knowledge of Cholesterol Metabolism 717
- IRONS, E E Chronic Arthritis, a General Disease Requiring Individualized Treatment 1658
- IRWIN, D The Experimental and Pathological Aspects of Silicosis 540
- JACKSON, H, JR Agranulocytosis 26
- JAMESON, E M Gynecological and Obstetrical Tuberculosis *Rev* 997
- JOHN, H J Diabetic Manual for Patients *Rev* 211
- JOHNSTON, T B Synopsis of Regional Anatomy *Rev* 810

- KANNFR, L Child Psychiatry *Rev* 211
- KAPLAN, M I, L FLIDMAN, I M
TRACE and— "Eventration" of the
Right Diaphragm Report of a Case
with Review of the Literature,
Chiefly from the Standpoint of Etiol-
ogy and Diagnosis 62
- KASSOWITZ, K E Around a World
on Fire *Rev* 1159
- KATZ, E, S L RUSKIN and— Thera-
peutic Action of the Nucleotides, the
Treatment of the Whole Blood Pic-
ture with Ferrous Adenylate 1549
- KELLOGG, F, N N EPSTEIN and W
J KERR Hepatic Complications in
the Treatment of Syphilis II In-
cidence of Hepatic Disease in Pa-
tients with Untreated Syphilis and
during Their Subsequent Treatment 1561
- KELLY, H A, H THOMAS and— Clas-
sical Contributions to Obstetrics and
Gynecology *Rev* 996
- KELLY, H T, J T BRADWOOD, JR
and— Simplified Diabetic Manage-
ment *Rev* 97
- KEMP, J E, W C MENNINGER and
— The Incidence of the Clinical
Types of Syphilis in Males, in Preg-
nant and Non-Pregnant Females 175
- KERR, W J, F KELLOGG, N N EP-
STEIN and— Hepatic Complications
in the Treatment of Syphilis II
Incidence of Hepatic Disease in Pa-
tients with Untreated Syphilis and
during Subsequent Treatment 1561
- KIDD, J G Instant Death in Bac-
terial Endocarditis Report of a Case
with Mycotic Ulceration of the Con-
duction System *Case Rep* 78
- KINSMAN, J M and J W MOORE
The Hemodynamics of the Circula-
tion in Hypertension 649
- KIRKLIN, B R and H A BURCH
Incidence and Significance of the
Roentgenologic Niche in Duodenal
Ulcer 436
- KOENIG, E C and B D BOWEN, E
C BECK, J G FOWLER,— Vascular
Disease in the Obese Diabetic, and
in Non-Diabetics, A Discussion of
Arteriosclerosis as a Cause of Dia-
betes 662
- LAMB, M E, H J BARST, J A FOITY
and— Gonorrheal Septicemia and
Erythema Nodosum *Case Rep* 790
- LANDIS, E M and L H HITZROT
Treatment of Peripheral Vascular
Disease by Means of Suction and
Pressure 264
- LONDON, J F and L W SMITH
Polioenclitis, a Handbook for Phy-
sicians and Medical Students *Rev* 808
- LARTSCHNEIDER, J Krebs—im Lichte
biologischer und vergleichend ana-
tomischer Forschung I Band
Rev 1607
- LAWRENCE, C H Adolescent Dis-
turbances of Endocrine Function, the
Importance of Their Recognition and
Treatment 1503
- LAWRENCE, J S, D J STEPHENS and
— Cyclical Agranulocytic Angina 31
- LAWRENCE, J S, D J STEPHENS and
— The Therapeutic Effect of So-
lution of Potassium Arsenite in
Chronic Myelogenous Leukemia 1488
- LEE, R I Hypothyroidism A Com-
mon Symptom 712
- LEINOFF, H D Splenic Vein Throm-
bosis and Its Relationship to Banti's
Syndrome, with Report of a Case
Case Rep 85
- LEMMANN, I I Subacute Bacterial
Endocarditis of the Mitral Valve
Previously Rendered Incompetent by
Infarction of the Papillary Muscle
and Shortening of the Chordae Ten-
dinæ *Case Rep* 1587
- LEOPOLD, S S and L M LIEBERMAN
The Present Status of Artificial
Pneumothorax in the Treatment of
Lobar Pneumonia 19
- LEWIS, G M and W SACHS Lipoi-
dal Histiocytoma (Fibroxanthoma)
Case Rep 1746
- LIEBERMAN, L M, S S LEOPOLD and
— The Present Status of Artificial
Pneumothorax in the Treatment of
Lobar Pneumonia 19
- LINDSAY, L M, A ROSS and F W
WIGGLESWORTH Von Gierke's Gly-
cogen Disease 274
- LISSER, H, R B ESCAMILLA,—and
H C SHEPARDSON Internal Mye-
dema, Report of a Case Showing As-
cites, Cardiac, Intestinal and Bladder

- Atony, Menorrhagia, Secondary Anemia and Associated Carotinemia 297
- LOBB, L The Thyroid Stimulating Hormone of the Anterior Pituitary Gland 13
- LONG, C N H Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism 1619
- LONG, C N H Recent Advances in Carbohydrate Metabolism with Particular Reference to Diabetes Mellitus 166
- LORD, F T and R HEFFRON Lobar Pneumonia and Serum Therapy *Rev* 1756
- LYNCH, C, G M BLECH and— Medical Tactics and Logistics *Rev* 1440
- LYON, B B V An Instance of Possible Cirrhosis of the Liver Induced by a Hair Tonic Containing Carbon Tetrachloride *Case Rep* 470
- LYON, B B V Differential Diagnosis of Diseases of the Liver 258
- MACEachern, M T Hospital Organization and Management *Rev* 642
- MANGES, W F Accessory Sinus Infection, Its Relation to Mastoid and Lung Infections 547
- MANN, F C, J L BOLLMAN and— Alterations in Hepatic Function Produced by Experimental Hepatic Lesions 617
- MARCUS, I H and J WEINSTEIN Dermatomyositis, Report of a Case with a Review of the Literature 406
- MARTIN, F H Fifty Years of Medicine and Surgery *Rev* 642
- MARTINI, P Principles and Practice of Physical Diagnosis *Rev* 642
- MASON, E C, P PAXTON and H A SHOEMAKER A Comparison of the Rate of Absorption from Normal and Burned Tissues 850
- MASON, M F, S S RIVEN and— Adenoma of the Parathyroid Gland, with Hyperparathyroidism *Case Rep* 1578
- MAYER, O B Enteric Cysts *Case Rep* 797
- MCCANN, W S Etiology of the Pulmonary Fibroses and Medico-Legal Aspects of Pneumonokoniosis 234
- McEachern, D, E C ANDRUS and— Studies on the Increased Metabolism in Hyperthyroidism 579
- McGEE, L C Blood Cholesterol in Disturbances of the Basal Metabolic Rate 728
- McKHANN, C F, A A GREEN, L E ECKLES and J A V DAVIES Immunological Applications of Placental Extracts, Effectiveness by Oral Administration 388
- McLESTER, J S Diagnosis and Treatment of Disorders of Metabolism *Rev* 1159
- MEAKINS, J C Presidential Address 1
- MENNINGER, W C and J E KEMP The Incidence of the Clinical Types of Syphilis in Males, in Pregnant and Non-Pregnant Females 175
- MILHORAT, A T and H G WOLFF Metabolism of Creatine and Creatinine in Muscle Disease 834
- MILLER, J A Pulmonary Fibrosis and Emphysema 219
- MILLER, J A The Changing Order in Medicine 1287
- MONTE, L A, E HULL and— The Treatment of Acute Mercuric Chloride Poisoning 54
- MOORE, J W, J M KINSMAN and— The Hemodynamics of the Circulation in Hypertension 649
- MOSENTHAL, H O The Diagnosis and Treatment of Variations in Blood Pressure and Nephritis *Rev* 1754
- NELSON, G M, M E RHFUSS and— The Medical Treatment of Gall Bladder Disease *Rev* 1755
- OCHSNER, H C and J A BARGEN Diverticulosis of the Large Intestine, An Evaluation of Historical and Personal Observations 282
- OSBORNE, O T Mouth Infection *Rev* 997
- OSGOOD, E E, M F GOURLEY and R L BAKER Diagnosis of Dissecting Aneurysm of the Aorta 1398
- PACE, I H Terminal Hemorrhagic Nephritis A Case Exemplifying the Protean Character of Its Signs and Symptoms *Case Rep* 1419

- PARDI, H. E. B. What You Should Know about Heart Disease *Rev* 1607
- PARSONNET, A. E. Paroxysmal Ventricular Tachycardia, Report of a Case Illustrating all the Accepted Diagnostic Criteria *Case Rep* 1258
- PARSONS, W. B., A. L. BARACH, D. W. RICHARDS and— Oxygen Treatment and Thyroid Ablation in the Treatment of Heart Disease 1513
- PANTON, P., E. C. MASON, —and H. A. SHOFMAKER. A Comparison of the Rate of Absorption from Normal and Burned Tissues 850
- PIMBERTON, J. DEJ. P. W. BROWN and — Solitary Ulcer of the Ileum and Ulcer of Meckel's Diverticulum 1684
- PINNER, M. The Mechanisms of Healing in Collapse Therapy 501
- POTTER, P. S. Pediatric Treatment *Rev* 997
- POWER, M. H., M. ADAMS, —and W. M. BOOTHBY. Chemical Studies in Myasthenia Gravis 823
- POWER, M. H., M. ADAMS —and W. M. BOOTHBY. Metabolism Studies in Myasthenia Gravis before and during the Administration of Glycine 1330
- PREU, P. W. and A. J. GEIGER. Symptomatic Psychoses in Pernicious Anemia 766
- PRINZ, H. and S. S. GREENBAUM. Diseases of the Mouth and Their Treatment *Rev* 811
- PUSEY, W. A. Disease, Gadfly of the Mind *Rev* 96
- PUTNAM, T. J. Studies in Multiple Sclerosis. VIII. Etiologic Factors in Multiple Sclerosis 854
- RABINOWITZ, M. A., C. SHOOKHOFF, A. H. DOUCIAS and— Sedimentation Time in Acute Cardiac Infarction 1101
- RAFASKY, H. A., A. BERNHARD and G. L. ROHDENBURG. Studies in Hypertension, A Proposed Classification of Hypertension Based Upon the Nitrogen Distribution of the Serum Proteins 1091
- REINROSS, M. E. and G. M. NELSON. The Medical Treatment of Gall Bladder Disease *Rev* 1755
- REINHART, E. C. and E. C. REINHART, JR. The Treatment of Addison's Disease with Sodium Compounds, with the Report of One Case and the Summaries of Eleven Other Collected Cases Thus Treated 1338
- RICHARDS, D. W., A. L. BARACH —and W. B. PARSONS. Oxygen Treatment and Thyroid Ablation in the Treatment of Heart Disease 1513
- RICHTER, A. B. Prognosis in Acute Glomerular Nephritis 1057
- RIMMEL, F. A. Allergic Coryza at Menstruation from Ovarian Hormone *Case Rep* 91
- RISMAN, D. The Story of Medicine in the Middle Ages *Rev* 491
- RISMAN, D. Tonsillitis Associated with Acute Aseptic Meningitis *Case Rep* 1427
- RINFHART, J. F. Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis, Experimental, Clinical, and General Considerations
I Rheumatic Fever 586
II Rheumatoid (Atrophic) Arthritis 671
- RITCHIE, W. T., J. COWAN and— Diseases of the Heart *Rev* 1607
- RIVEN, S. S. and M. F. MASON. Adenoma of the Parathyroid Gland, with Hyperparathyroidism *Case Rep* 1578
- RIVERS, T. M. Viruses and the Diseases Caused by Them 1466
- ROBERTS, G. H. and D. I. ABRAMSON. Ventricular Complexes of the Bundle-Branch-Block Type Associated with Short P-R Intervals *Case Rep* 983
- ROBERTS, J. F. Renal Dwarfism *Case Rep* 1729
- ROBERTSON, H. F., J. B. WOLFF and — Experimental Air Embolism 162
- RODDIS, L. H. Schiller, the Greatest of the Medical Poets 1240
- ROEHM, H. R. Primary Costal Osteomyelitis *Case Rep* 200
- ROESLER, H. and L. A. SOLOFF. Report of a Case of Left Ventricular Failure with Unusual Anatomical Changes in the Myocardium *Case Rep* 477
- ROHDENBURG, G. L., H. A. RAFASKY, A. BERNHARD and— Studies in Hypertension. A Proposed Classification of Hypertension Based upon the

- Nitrogen Distribution of the Serum Proteins 1091
- ROOT, H F and T P SHARPE Arteriosclerosis and Hypertension in Diabetes 873
- ROSE, W D, W P ELMER and— Physical Diagnosis *Rev* 492
- ROSS, A, L M LINDSAY, —and F W WIGGIESWORTH Von Gierke's Glycogen Disease 274
- ROTH, G M and C H WATKINS The Leukocyte Picture in Hodgkin's Disease 1365
- ROTHSTEIN, E, B BURBANK and— Artificial Pneumothorax in the Treatment of Lobar Pneumonia 376
- ROWNTREE, L G, J H CLARK, A STEINBERG, A M HANSON, N H EINHORN and W A SHANNON Further Studies on the Thymus and Pineal Glands 359
- RUSKIN, S L and E KATZ Therapeutic Action of the Nucleotides, the Treatment of the Whole Blood Picture with Ferrous Adenylate 1549
- SACHS W, G W LEWIS and— Lipoidal Histiocytoma (Fibroxanthoma) *Case Rep* 1746
- SANFORD, C H Pernicious Anemia with Normal Blood Picture 189
- SAULS, H C, C SMITH and— Recovery from Coronary Thrombosis, Report of Eight Cases, with Particular Reference to the Recognition of the Less Severe and Atypical Types 317
- SCHNABEL, T G and F FETTER Fever Therapy in Gonorrheal Arthritis and Chorea 398
- SEWARD, B P A Clinical Study of the Mild Grades of Hypothyroidism 178
- SHANNON, W A, L G ROWNTREE, J H CLARK, A STEINBERG, A M HANSON, N H EINHORN, and— Further Studies on the Thymus and Pineal Glands 359
- SHARPE, T P, H F ROOT and— Arteriosclerosis and Hypertension in Diabetes 873
- SHARPE, J C Intermittent Hydrarthrosis Associated with Undulant Fever *Case Rep* 1431
- SHAY, H and J GERSHON-COHEN A Comparison of the Effectiveness of Glutamic Acid Hydrochloride and Dilute Hydrochloric Acid as the Replacement Therapy in Anacidity Measured by Fractional Gastric Acid Titration and Hydrogen-Ion Concentration Curves 1628
- SHFLBURN, S A Primary Tumors of the Heart, with Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis before Death *Case Rep* 340
- SHEPARDSON, H C, R F ESCAMILLA, H LISSER and— Internal Myxedema, Report of a Case Showing Ascites, Cardiac, Intestinal and Bladder Atony, Menorrhagia, Secondary Anemia and Associated Carotinemia 297
- SHERMAN, H C Food and Health *Rev* 353
- SHOEMAKER, H A, E C MASON, P PAXTON and— A Comparison of the Rate of Absorption from Normal and Burned Tissues 850
- SHOOKHOFF, C, A H DOUGLAS and M A RABINOWITZ Sedimentation Time in Acute Cardiac Infarction 1101
- SIGLER, L H Further Observations on the Carotid Sinus Reflex 1380
- SIMMONS, J S and C J GENTZKOW (Editors) Laboratory Methods of the United States Army *Rev* 1268
- SKAVLEM, J H, K DUNHAM and— Basic Points in Roentgen-Ray Studies of Lung Anatomy and Pathology 555
- SMITH, C and H C SAULS Recovery from Coronary Thrombosis, Report of Eight Cases, with Particular Reference to the Recognition of the Less Severe and Atypical Types 317
- SMITH, L W, J F LONDON and— Poliomyelitis, a Handbook for Physicians and Medical Students *Rev* 808
- SNELL, A M The Effects of Chronic Disease of the Liver on the Composition and Physicochemical Properties of Blood Changes in the Serum Proteins, Reduction in the Oxygen Saturation of the Arterial Blood 690
- SOLOFF, L A, H ROESLER and— Report of a Case of Left Ventricular

- Failure with Unusual Anatomical Changes in the Myocardium *Case Rep* 477
- SOPFR, H W, J W THOMPSON and— Combined Medical and Surgical Management of Peptic Ulcer, with Emphasis on the Treatment of Hemorrhage 1106
- SPURLING, R G Practical Neurological Diagnosis, with Special Reference to the Problems of Neurosurgery *Rev* 1158
- STARR, I, JR, and C J GAMBLE Cardiac Output in Common Clinical Conditions, and the Diagnosis of Myocardial Insufficiency by Cardiac Output Methods 569
- STEINBERG, A, A M HANSON, N H LINHORN, and W A SHANNON, L G ROWNTRFF, J H CLARK,— Further Studies on the Thymus and Pineal Glands 359
- STEINBROCKER, O, E F HARTUNG and— Gastric Acidity in Chronic Arthritis 252
- STEPHENS, D J and J S LAWRENCE Cyclical Agranulocytic Angina 31
- STEPHENS, D J and J S LAWRENCE The Therapeutic Effect of Solution of Potassium Arsenite in Chronic Myelogenous Leukemia 1488
- STRAUSS, M B The Etiology and Prevention of Anemia in Pregnancy 38
- STRAYER, J W, P D CRIMM and— Phosphatase Content of Human Serum in Pulmonary Tuberculosis Following the Administration of Vitamin D 1393
- SULLIVAN, A I, G BLUMER and— The Practitioner's Library of Medicine and Surgery Vol VIII Therapeutics *Rev* 210
- SWEET, M H, J C HEALY,—and F P CHILLINGWORTH Effect of Vibratory Stimulation on the Neutrophilic Index 123
- THOMPSON, J W and H W SOPER Combined Medical and Surgical Management of Peptic Ulcer, with Emphasis on the Treatment of Hemorrhage 1106
- THOMS, H and H A KELLY Classical Contributions to Obstetrics and Gynecology *Rev* 996
- THOMSON, D L Correlations of the Endocrine System 864
- TOCANTINS, L M Experimental Thrombopenic Purpura, Cytological and Physical Changes in the Blood 838
- TRACE, I M, L FELDMAN,—and M I KAPLAN "Eventration" of the Right Diaphragm Report of a Case with Review of the Literature, Chiefly from the Standpoint of Etiology and Diagnosis 62
- TRAPP, C E, H ULRICH,—and B VINGOFF The Treatment of Narcolepsy with Benzedrine Sulphate 1213
- ULRICH, H, C E TRAPP and B VINGOFF The Treatment of Narcolepsy with Benzedrine Sulphate 1213
- UNGAR, J, V B CALLEMON and— Treatment of Pneumonia with Serum Containing Type-Specific, Heterophile, and Neutralizing Antibodies 1664
- VINGOFF, B, H ULRICH, C E TRAPP and— The Treatment of Narcolepsy with Benzedrine Sulphate 1213
- WAINWRIGHT, C W Treatment of Chronic Rheumatoid Arthritis, Further Observations on the Use of Streptococcal Vaccine 245
- WAKEFIELD, E G and S C DELLINGER A Report of Identical Albino Twins of Negro Parents *Case Rep* 1149
- WAKEFIELD, E G and S C DELLINGER Diet of the Bluff Dwellers of the Ozark Mountains and Its Skeletal Effects 1412
- WALDBOTT, G L and M S ASCHER The Role of Accidental Puncture of Veins in the Production of Allergic Shock 1232
- WALKER, H The Etiology of Abdominal Pain in Diabetic Acidosis 1178
- WALLFIELD, M J, M B GORDON and — Toxic Reaction to Alpha-Dinitro-Ortho-Cresol *Case Rep* 198
- WATKINS, C H, G M ROTH and— The Leukocyte Picture in Hodgkin's Disease 1365

- WEINSTEIN, J and D I ABRAMSON
Localization of the Site of Experimental Premature Contractions and Bundle Branch Lesions by Means of Multiplane Chest Leads 1187
- WEINSTEIN, J, I H MARCUS and—
Dermatomyositis, Report of a Case with a Review of the Literature 406
- WEISMAN, S A The Relationship of the Flat Chest to Intelligence 451
- WEISS, S Diseases of the Liver, Gall Bladder, Ducts and Pancreas *Rev* 1441
- WHITBY, L E H and C J C BRITTON
Disorders of the Blood *Rev* 1441
- WHITE, P D Errors in the Interpretation of Cardiovascular Symptoms and Signs 1703
- WHITE, P D The Acute Cor Pulmonale 115
- WHITE, T P, P S HENCH, W BAUER, A A FLETCHER, D GHRIST, F HALL and—
The Present Status of the Problem of "Rheumatism" and Arthritis, Review of American and English Literature for 1934 883
- WIENER, A S Blood Groups and Blood Transfusion *Rev* 490
- WIGGLESWORTH, F W, L M LINDSAY, A ROSS and—
Von Gierke's Glycogen Disease 274
- WILLIAMS, F H Radium Treatment of Skin Diseases, New Growths, Diseases of the Eyes and Tonsils *Rev* 996
- WILLIAMS, R H Felty's Syndrome, Report of a Case with Necropsy Findings *Case Rep* 1247
- WISEMAN, B K Lymphopoiesis, Lymphatic Hyperplasia, and Lymphemia Fundamental Observations Concerning the Pathologic Physiology and Interrelationships of Lymphatic Leukemia, Leukosarcoma and Lymphosarcoma 1303
- WOLFF, H G, A T MILHORAT and—
Metabolism of Creatine and Creatinine in Muscle Disease 834
- WOLFFE, J B and H F ROBERTSON
Experimental Air Embolism 162
- WORCESTER, A The Care of the Aged, The Dying, and the Dead *Rev* 97
- WOSIKA, P H and E S ENFERY, JR
The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice of Patients If the Amount of Alkali Is Not Varied 1070
- WOSIKA, P H and E S ENERY, JR
The Value of a Mixture of Powdered Milk and Alkali for Neutralizing the Gastric Acidity of Patients with Peptic Uleer 1078
- YATER, W M Non-Traumatic Chylothorax and Chylopericardium, Review and Report of a Case Due to Carcinomatous Thromboangitis Obliterans of the Thoracic Duct and Upper Great Veins 600
- ZONDER, H The Diseases of the Endocrine Glands *Rev* 1160

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 9, 1935-1936

- A**BDOMINAL Distention in Lobar Pneumonia J GOLDMAN and A COHEN 1222
- Abdominal Pain in Diabetic Acidosis, The Etiology of— H WALKER 1178
- Absorption, A Comparison of the Rate of—from Normal and Burned Tissues E C MASON, P PAXTON and H A SHOFMAKER 850
- Accessory Sinus Infection, Its Relation to Mastoid and Lung Infections W F MANGES 547
- Acetyl-B-Methylcholine Given by Mouth as a Vasodilating Agent, The Effectiveness of— G A GOLDSMITH 1196
- Acute Lymphatic Leukemia in a Child of Four Years with a Severe Granulopenic Phase Preceding a Remission L B FLINN 458
- Addison's Disease, The Importance of Potassium in the Treatment of— *Edit* 1752
- Addison's Disease, The Treatment of—with Sodium Compounds, with the Report of One Case and the Summaries of Eleven Other Collected Cases Thus Treated E C REIFFENSTEIN and E C REIFENSTEIN, JR 1338
- Adenoma of the Parathyroid Gland, with Hyperparathyroidism S S RIVEN and M F MASON *Case Rep* 1578
- Adolescent Disturbances of Endocrine Function, the Importance of Their Recognition and Treatment C H LAWRENCE 1503
- Adrenals, Acute Fulminating Meningococcus Infection, with Bilateral Capillary Hemorrhage of the—as the Most Striking Gross Pathologic Lesion F H FOUCAR *Case Rep* 1736
- Aged, The Care of the—, the Dying, and the Dead A WORCESTER *Rev* 97
- Agranulocytic Angina, Cyclic— D J STEPHENS and J S LAWRENCE 31
- Agranulocytosis H JACKSON, JR 26
- Albino Twins of Negro Parents, A Report of Identical— E G WAKELIN and S C DILLINGER *Case Rep* 1149
- Allergic Coryza at Menstruation from Ovarian Hormone F A RIBBEN *Case Rep* 91
- Allergic Shock The Role of Accidental Puncture of Veins in the Production of— G L WAINBROT and M S ASCHER 1232
- Allergy, Recent Advances in— G W BRAY *Rev* 808
- Alpha-Dinitro-Ortho-Cresol, Toxic Reaction to— M B GORDON and M J WAINFIELD 198
- Amebiasis and Amebic Dysentery C F CRAIG *Rev* 492
- American Board of Internal Medicine, The— *Edit* 1751
- Anacidity Measured by Fractional Gastric Acid Titration and Hydrogen-Ion Concentration Curves, A Comparison of the Effectiveness of Glutamic Acid Hydrochloride and Dilute Hydrochloric Acid as the Replacement Therapy in— H SHAY and J GERSON-CONYEN 1628
- Anatomy Synopsis of Regional— T B JOHNSTON *Rev* 810
- Anemia, Neurological Symptoms in Posthemorrhagic Secondary— S B HADNAN 1572
- Anemia, Pernicious—with Normal Blood Picture C H SANIORD 189
- Anemia, Symptomatic Psychoses in Pernicious— P W PRU and A J GEIGER 766
- Anemia in Pregnancy, The Etiology and Prevention of— M B STRAUSS 38
- Aneurysm of the Aorta, Diagnosis of Dissecting— E E OSGOOD, M F GOURLY and R L BAKER 1398
- Angina Pectoris, Observations on the Effect of Sudden Changes in Arterial Tension in— E W BITZER 1120

- Anti-Hormones, Recent Studies on—
J B COLLIP 150
- Aorta, Diagnosis of Dissecting Aneurysm of the— E E OSGOOD, M F GOURLEY and R L BAKER 1398
- Arsenite, The Therapeutic Effect of Solution of—in Chronic Myelogenous Leukemia D J STPLHLNS and J S LAWRENCE 1488
- Arterial Tension in Angina Pectoris, Observations on the Effect of Sudden Changes in— E W BITZFER 1120
- Arteries, Synopsis of Diseases of the Heart and— G R HERRMAN *Rev* 1754
- Arteriosclerosis and Hypertension in Diabetes H F ROOT and T P SHARKEY 873
- Arteriosclerosis as a Cause of Diabetes, Vascular Disease in the Obese Diabetic, and in Non-Diabetics, A Discussion of— E C BECK, J G FOWLER, E C KOENIG and B D BOWEN 662
- Arthritis, Chronic—, a General Disease Requiring Individualized Treatment E E IRONS 1658
- Arthritis, Gastric Acidity in Chronic — E F HARTUNG and O STEIN-BROCKER 252
- Arthritis, Rheumatoid—, Studies Relating Vitamin C Deficiency to Rheumatic Fever and—, Experimental, Clinical and General Considerations J F RINEHART
I Rheumatic Fever 586
II Rheumatoid (Atrophic) Arthritis 671
- Arthritis, The Present Status of the Problem of "Rheumatism" and— Review of American and English Literature for 1934 P S HENCH W BAUER, A A FLETCHER, D GHRIST, F HALL and T P WHITE 883
- Arthritis, Treatment of Chronic Rheumatoid—, Further Observations on the Use of Streptococcal Vaccine C W WAINWRIGHT 245
- Arthritis and Chorea, Fever Therapy in Gonorrheal— T G SCHNABEL and F FETTER 398
- Artificial Pneumothorax in the Treatment of Lobar Pneumonia B BURBANK and E ROTHSTEIN 376
- Artificial Pneumothorax in the Treatment of Lobar Pneumonia, The Present Status of— S S LEOPOLD and L M LIEBERMAN 19
- Asthma, The Present Status of Bronchoscopy in Bronchial— L H CLIFFE 1050
- Asthma and Obstructive Lesions in the Larynx and Trachea, The Use of Helium in the Treatment of— A L BARACH 739
- Auricular Fibrillation with Organic Heart Disease, Long-Standing Cases of—, Some Clinical Considerations W A EVANS 1171
- B**ACTERIAL Endocarditis Instant Death in— Report of a Case with Mycotic Ulceration of the Conduction System J G KIDD *Case Rep* 78
- Banti's Syndrome, Splenic Vein Thrombosis and Its Relationship to —, with Report of a Case H D LEINOFF *Case Rep* 85
- Basal Metabolic Rate, Blood Cholesterol in Disturbances of the— L C MCGEE 728
- Behavior Development in Infants, a Survey of the Literature on Pre-Natal and Post-Natal Activity, 1920-1934 E DEWEY *Rev* 1158
- Benzedrine Sulphate, The Treatment of Narcolepsy with— H ULRICH, C E TRAPP and B VINGOFF 1213
- Blackwater Fever A Clinical Review of Fifty-Two Cases M FERNAN-NUÑEZ 1203
- Blood, Disorders of the— L E H WHITBY and C J C BRITTON *Rev* 1441
- Blood Cholesterol, Clinical Relationships of—with a Summary of Our Present Knowledge of Cholesterol Metabolism L M HURVITZ and H M HUNT 717
- Blood Cholesterol in Disturbances of the Basal Metabolic Rate L C MCGEE 728
- Blood Groups and Blood Transfusion A S WISNER *Rev* 490
- Blood Pressure, Posture and— *Edit* 638
- Blood Pressure and Nephritis, The Diagnosis and Treatment of Variations in— H O MOSFATHAI

- Rev* 1754
 Blood Vessels and Lymphatics, Growth and Development of Function in— E R CLARK 1043
 Body Water, The Movement and Distribution of— *Edit* 806
 Bronchomoniliasis, A Study of Nine Cases of— J W FLINN, R S FLINN and Z M FLINN 42
 Bronchoscopy in Bronchial Asthma, The Present Status of— L II CLERI 1050
 Brucella Infections in Animals and Man Methods of Laboratory Diagnosis I F HUNNIFSON *Rev* 212
 Bundle-Branch-Block Type, Ventricular Complexes of the—Associated with Short P-R Intervals G H ROBERTS and D I ABRAMSON *Case Rep* 983
 Bundle Branch Lesions, Localization of the Site of Experimental Premature Contractions and—by Means of Multiphase Chest Leads J WEINSTEIN and D I ABRAMSON 1187
- C**ARBOHYDRATE Metabolism, Recent Advances in—with Particular Reference to Diabetes Mellitus C N H LONG 166
 Carbon Tetrachloride, An Instance of Possible Cirrhosis of the Liver Induced by a Hair Tonic Containing— B B V LYON *Case Rep* 470
 Cardiac Infarction, Sedimentation Time in Acute— C SHOOKHOFF, A H DOUGLAS and M A RABINOWITZ 1101
 Cardiac Output in Common Clinical Conditions, and the Diagnosis of Myocardial Insufficiency by Cardiac Output Methods I STARR, JR, and C J GAMBLE 569
 Cardiovascular Symptoms and Signs, Errors in the Interpretation of— P D WHITE 1703
 Care of the Aged, the Dying, and the Dead, The— A WORCESTER *Rev* 97
 Carotid Sinus Reflex, Further Observations on the— L H SIGLER 1380
 Cataracts, Dimetrophenol and Rapidly Developing— W W BOARDMAN *Case Rep* 195
 Chemical Studies in Myasthenia
- Gravis M ADAMS, M H POWIE and W M BOOTHBY 823
 Child Psychiatry L KANNER *Rev* 211
 Cholesterol, Blood—in Disturbances of the Basal Metabolic Rate L C MCGEE 728
 Cholesterol, Clinical Relations of Blood—with a Summary of Our Present Knowledge of Cholesterol Metabolism L M HURNTHAL and H M HUNT 717
 Chorea, Fever Therapy in Gonorrheal Arthritis and— T G SCHNABFI and F FETTER 398
 Chylopericardium, Non-Traumatic Chylothorax and—, Review and Report of a Case Due to Carcinomatous Thromboangitis Obliterans of the Thoracic Duct and Upper Great Veins W M YATTE 600
 Circulatory Failure, The Beneficial Effect of the Development of an Abnormal Rhythm with Slow Ventricular Rate in— W C COOK *Case Rep* 1143
 Cirrhosis of the Liver Induced by a Hair Tonic Containing Carbon Tetrachloride, An Instance of Possible — B B V LYON *Case Rep* 470
 Classical Contributions to Obstetrics and Gynecology H THOMAS and H A KELLY *Rev* 996
 Clinical Laboratory Medicine and Diagnosis R B H GRADWOHL *Rev* 490
 Clinical Laboratory Methods P S DIMMITT *Rev* 1606
 Clinical Management of Syphilis A R HARNES *Rev* 353
 Clinical Types of Syphilis in Males, The Incidence of the—, in Pregnant and Non-Pregnant Females W C MENNINGER and J E KEMP 175
 Collapse Therapy, The Mechanisms of Healing in— M PINNER 501
 Cor Pulmonale, The Acute— P D WHITE 115
 Coronary Thrombosis, Recovery from —, Report of Eight Cases, with Particular Reference to the Recognition of the Less Severe and Atypical Types C SMITH and H C SAULS 317
 Coronary Thrombosis, The Initial Ventricular Complex of the Electrocardiogram in— L FELDMAN 1714

- Creatine and Creatinine in Muscle Disease, Metabolism of— A T MILLORAT and H G WOLFF 834
- Crime, Roots of— Psychoanalytic Studies F ALEXANDER and W HEALY *Rev* 354
- Cumming, Surgeon General—Retires from Active Duty *Edit* 1604
- Cyclical Agranulocytic Angina D J STEPHENS and J S LAWRENCE 31
- Cysts, Enteric— O B MAYER *Case Rep* 797
- D**ERMATOMYOSITIS, Report of a Case with Review of the Literature I H MARCUS and J WEINSTEIN 406
- Detroit and Ann Arbor Sessions, The— *Edit* 1266
- Diabetes, Arteriosclerosis and Hypertension in— H F ROOT and T P SHARKEY 873
- Diabetes, Vascular Disease in the Obese Diabetic, and in Non-Diabetics, A Discussion of Arteriosclerosis as a Cause of— E C BECK, J G FOWLER, E C KOENIG and B D BOWEN 662
- Diabetes Mellitus, Recent Advances in Carbohydrate Metabolism with Particular Reference to— C N H LONG 166
- Diabetes Mellitus and Obesity G G DUNCAN *Rev* 641
- Diabetes Refractory to Insulin S S ALTSHULFR and S E GOULD *Case Rep* 1595
- Diabetic Acidosis, The Etiology of Abdominal Pain in— H WALKER 1178
- Diabetic Coma with Acute Renal Failure, Fatal— M E HOLMES 426
- Diabetic Gangrene, Excessive Smoking as a Possible Precipitating Factor in—, with a Case Report H BLONER *Case Rep* 987
- Diabetic Management, Simplified— J T BEARDWOOD, JR, and H T KELL *Rev* 97
- Diabetic Manual for Patients J H JOHN *Rev* 211
- Diagnosis and Treatment of Disorders of Metabolism J S MCLESTER *Rev* 1159
- Diagnosis, of Dissecting Aneurysm of the Aorta E E OSGOOD, M F GOURLEY and R L BAKER 1398
- Diaphragm, "Eventration" of the Right— Report of a Case with Review of the Literature, Chiefly from the Standpoint of Etiology and Diagnosis L FELDMAN, I M TRACF and M I KAPLAN 62
- Dict, Treatment by— C J BARBORKA *Rev* 97
- Diet of the Bluff Dwellers of the Ozark Mountains and Its Skeletal Effects E G WAKEFIELD and S C DELINGER 1412
- Dietetics for the Clinician M A BRIDGES *Rev* 210
- Differential Diagnosis of Diseases of the Liver B B V LYON 258
- Dinitrophenol and Rapidly Developing Cataracts W W BOARDMAN *Case Rep* 195
- Disease, Gaffly of the Mind W A PUSEY *Rev* 96
- Diseases of the Endocrine Glands, The — H ZONDER *Rev* 1160
- Diseases of the Liver, Gall Bladder, Ducts and Pancreas S WEISS *Rev* 1441
- Diseases of the Mouth and Their Treatment H PRINZ and S S GREENBAUM *Rev* 811
- Diseases of the Nervous System W R BRAIN *Rev* 641
- Diseases of the Thyroid Gland A E HERIZLER *Rev* 809
- Disorders of the Blood L E H WHITBY and C J C BRITTON *Rev* 1441
- Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism C N H LONG 1619
- Diverticulosis of the Large Intestine, an Evaluation of Historical and Personal Observations H C OCHSNER and J A BARGEN 282
- Diverticulum, Solitary Ulcer of the Ileum and Ulcer of Meckel's— P W BROWN and J DEJ PFEMBERTON 1684
- Duodenal Ulcer, Incidence and Significance of the Roentgenologic Niche in— B R KIRKLIN and H A BURCH 436
- Duodenum, The Stomach and— G

- B EUSTERMANN and D C BATHOR *Rev* 1755
- Dwarfism, Renal— J F ROBERTS *Case Rep* 1729
- E** DUCATION and Medical Institutions in Michigan, Notes on Medical— 1024
- Embolism Experimental Air— J B WOLFE and H F ROBERTSON 162
- Emotion in Disease, The Role of— W B CANNON 1453
- Emotions and Bodily Changes *Edit* 93
- Emphysema, Pulmonary Fibrosis and — J A MILLER 219
- Encephalitis Lethargica, Late Recrudescence in—with Succession of New Manifestations at Intervals of Years, the Problem of Prognosis A GORDON 1725
- Endocarditis, Instant Death in Bacterial— Report of a Case with Mycotic Ulceration of the Conduction System J G KING *Case Rep* 78
- Endocarditis, Subacute Bacterial—of the Mitral Valve Previously Rendered Incompetent by Infarction of the Papillary Muscle and Shortening of the Chordae Tendinae I I LEMANN *Case Rep* 1587
- Endocrine Balance, Disturbances of the—and Their Relation to Diseases of Metabolism C N H LONG 1619
- Endocrine Function, Adolescent Disturbances of—, the Importance of Their Recognition and Treatment C H LAWRENCE 1503
- Endocrine Glands, The Diseases of the — H ZONDEK *Rev* 1160
- Endocrine System, Correlations of the — D L THOMSON 864
- Endocrines, Personality and the—, A Study Based upon 1400 Quantitative Necropsies W FREEMAN 444
- Endocrinology, Practical— Symptoms and Treatment M A GOIDZICHER *Rev* 1160
- Enteric Cysts O B MAYER *Case Rep* 797
- Erythema Nodosum, Gonorrheal Septicemia and— H J BAKST, J A FOLEY and M E LAMB *Case Rep* 790
- Etiology and Prevention of Anemia in Pregnancy, The— M B STRAUSS 38
- Etiology of the Pulmonary Fibroses and Medico-Legal Aspects of Pneumokoniosis W S MCCANN 234
- "Eventration" of the Right Diaphragm Report of a Case with Review of the Literature, Chiefly from the Standpoint of Etiology and Diagnosis L FRIEDMAN, I M TRACE and M I KAPLAN 62
- Experimental Air Embolism J B WOLFE and H F ROBERTSON 162
- Experimental and Pathological Aspects of Silicosis, The— D IRWIN 540
- Extremities, Lymphedema of the — Etiology, Classification and Treatment, Report of 300 Cases E V ALFEN and R K GHORMLEY 516
- F** ACTORS in the Falling Death Rate from Tuberculosis *Edit* 1154
- Fatal Diabetic Coma with Acute Renal Failure M E HOLMES 426
- Felty's Syndrome, Report of a Case with Necropsy Findings R H WILLIAMS *Case Rep* 1247
- Ferrous Adenylate, Therapeutic Action of the Nucleotides the Treatment of the Whole Blood Picture with — S L RUSKIN and E KATZ 1549
- Fever Therapy in Gonorrheal Arthritis and Chorea T G SCHNABEL and F FETTER 398
- Fire, Around a World on— K E KASSOWITZ *Rev* 1159
- Flat Chest, The Relationship of the— to Intelligence S A WEFISMAN 451
- Food and Health H C SHIFMAN *Rev* 353
- G** ALL Bladder Disease, The Medical Treatment of— M E REHFUSS and G M NELSON *Rev* 1755
- Gastric Acidity in Chronic Arthritis E F HARTUNG and O STEINBROCKER 252
- Gastric Acidity of Patients with Peptic Ulcer, The Value of a Mixture of Powdered Milk and Alkali for Neutralizing the— P H WOSIK and E S EMERY, JR 1078
- Gastric Juice, The Effectiveness of the Sippy Regimen in Neutralizing the —of Patients if the Amount of Al-

- kali Is Not Varied P H WOSIKA
and E S EMERY, JR 1070
- Gastrointestinal and Renal Disease, The
Interrelationship of— H GAUSS 1373
- Glutamic Acid Hydrochloride, A Com-
parison of the Effectiveness of—and
Dilute Hydrochloric Acid as the Re-
placement Therapy in Anacidity
Measured by Fractional Gastric Acid
Titration and Hydrogen-Ion Concen-
tration Curves H SHAY and J
GERSHON-COHEN 1628
- Glycine, Metabolism Studies in Myas-
thenia Gravis before and during the
Administration of— M ADAMS,
M H POWER and W M BOOTHBY 1330
- Glycogen Disease, Von Gierke's— L
M LINDSAY, A ROSS and F W
WIGGLESWORTH 274
- Gonorrheal Septicemia and Erythema
Nodosum H J BAKST, J A FOLEY
and M E LAMB *Case Rep* 790
- Granulopenic Phase Preceding a Re-
mission, Acute Lymphatic Leukemia
in a Child of Four Years with a
Severe— L B FLINN 458
- Gynecological and Obstetrical Tubercu-
losis E M JAMESON *Rev* 997
- Gynecology B M ANSPACH *Rev* 1606
- H**ARVEY Lectures, The— 1933-
1934 R E DYER, W M CLARK,
R G HARRISON, E A DOISY, E A
GRAHAM, G L STREETER, T M
RIVERS and D W BRONK *Rev* 97
- Heart, Diseases of the— J COWAN
and W T RITCHIE *Rev* 1607
- Heart, Primary Tumors of the —,
with Special Reference to Certain
Features Which Led to a Logical
and Correct Diagnosis before Death
S A SHELburnE *Case Rep* 340
- Heart and Arteries, Synopsis of Dis-
eases of the— G R HERRMANN
Rev 1754
- Heart Disease, Long-Standing Cases of
Auricular Fibrillation with Organic
—, Some Clinical Considerations
W A EVANS 1171
- Heart Disease, Oxygen Treatment and
Thyroid Ablation in the Treatment
of— A L BARACH, D W RICH-
ARDS and W B PARSONS 1513
- Heart Disease, What You Should
Know about— H E B PARDEE
Rev 1607
- Helium, The Use of—in the Treat-
ment of Asthma and Obstructive
Lesions in the Larynx and Trachea
A L BARACH 739
- Hemodynamics of the Circulation in
Hypertension, The— I M KINS-
MAN and J W MOORE 649
- Hemopoiesis, The Role of the Liver
in— *Edit* 992
- Hemorrhage, Combined Medical and
Surgical Management of Peptic Ul-
cer, with Emphasis on the Treat-
ment of— J W THOMPSON and
H W SOPER 1106
- Hemorrhagic Nephritis, Terminal— A
Case Exemplifying the Protean
Character of Its Signs and Sym-
ptoms I H PAGE *Case Rep* 1419
- Hepatic Complications in the Treat-
ment of Syphilis II Incidence of
Hepatic Disease in Patients with
Untreated Syphilis and during Their
Subsequent Treatment F KELLOGG,
N N EPSTEIN and W J KERR 1561
- Hepatic Function, Alterations in—
Produced by Experimental Hepatic
Lesions J L BOLLMAN and F
C MANN 617
- Hibbs, Russell A— G M GOODWIN
Rev 810
- Hobbies in the Practice of Medicine,
The Practical Use of— J R
HAMILTON 1129
- Hodgkin's Disease, The Leukocyte
Picture in— G M ROTH and C
H WATKINS 1365
- Hormone, Allergic Coryza at Men-
struation from Ovarian— F A
RIEBEL *Case Rep* 91
- Hormone, The Thyroid Stimulating—
of the Anterior Pituitary Gland L
LOEB 13
- Hormones Recent Studies on Anti-
Hormones J B COLLIP 150
- Hospital Organization and Manage-
ment M T MACEachERn *Rev* 642
- Hydrarthrosis, Intermittent—Associated
with Undulant Fever J C SHARFF
Case Rep 1431
- Hyperparathyroidism Adenoma of the
Parathyroid Gland with— S S
RIVIN and M F MASON *Case Rep* 1578

- Hypertension, Arteriosclerosis and—
Diabetes H F Root and T P
SHARKEY 873
- Hypertension, Studies in—, A Pro-
posed Classification of Hypertension
Based upon the Nitrogen Distribu-
tion of the Serum Proteins H A
RAFSKY, A BERNHARD and G L
ROHDENBURG 1091
- Hypertension, Surgical Procedures in
Essential— G E BROWN *Edit* 488
- Hypertension, The Hemodynamics of
the Circulation in— J M KINS-
MAN and J W MOORE 649
- Hyperthyroidism, Studies on the In-
creased Metabolism in— E C
ANDRUS and D McEACHERN 579
- Hypothyroidism, A Clinical Study of
the Mild Grades of— B P SWARD 178
- Hypothyroidism A Common Symp-
tom R I LEE 712
- I**LEUM, Solitary Ulcer of the—and
Ulcer of Meckel's Diverticulum
P W BROWN and J DEJ PEMBER-
TON 1684
- Immunological Applications of Placental
Extracts, Effectiveness by
Oral Administration C F Mc-
KHANN, A A GREEN, L E ECKLES
and J A V DAVIES 388
- Initial Ventricular Complex of the
Electrocardiogram in Coronary
Thrombosis, The— L FELDMAN 1714
- Insulin, Diabetes Refractory to— S
S ALTSHULER and S E GOULD
Case Rep 1595
- Insulin, Studies on— *Edit* 1437
- Intelligence, The Relationship of the
Flat Chest to— S A WEISMAN 451
- Intermittent Hydrarthrosis Associated
with Undulant Fever J C SHARPE
Case Rep 1431
- Internal Medicine, The American
Board of— *Edit* 1751
- Internal Myxedema, Report of a Case
Showing Ascites, Cardiac, Intestinal
and Bladder Atony, Menorrhagia,
Secondary Anemia and Associated
Carotinemia R F ESCAMILLA, H
LISSER and H C SHEPARDSON 297
- K**REBS—Im Lichte biologischer
und vergleichend anatomischer
Forschung I Band J LART-
SCHNEIDER *Rev* 1607
- L**ABORATORY Methods of the
United States Army J S
SIMMONS and C J GENTZKOW (Ed-
itors) *Rev* 1268
- Larynx and Trachea, The Use of He-
lium in the Treatment of Asthma
and Obstructive Lesions in the— A
L BARACH 739
- Left Ventricular Failure with Un-
usual Anatomical Changes in the
Myocardium, Report of a Case of—
H ROFSLER and L A SOLOFF *Case
Rep* 477
- Leukemia, Acute Lymphatic—in a Child
of Four Years with a Severe Granu-
lopenic Phase Preceding a Remis-
sion L B FLANN 458
- Leukemia, Leukosarcoma and Lympho-
sarcoma, Fundamental Observations
Concerning the Pathologic Physiol-
ogy and Interrelationships of Lym-
phatic— Lymphopoiesis, Lymphatic
Hyperplasia, and Lymphemia —
B K WISMAN 1303
- Leukemia, The Therapeutic Effect of
Solution of Potassium Arsenite in
Chronic Myelogenous— D J STE-
PHENS and J S LAWRENCE 1488
- Leukocyte Picture in Hodgkin's Dis-
ease, The— G M ROTH and C
H WATKINS 1365
- Lipoidal Histiocytoma (Fibroxan-
thoma) G M LEWIS and W
SACHS *Case Rep* 1746
- Liver, An Instance of Possible Cirrho-
sis of the—Induced by a Hair Tonic
Containing Carbon Tetrachloride B
B V LYON *Case Rep* 470
- Liver, Differential Diagnosis of Dis-
eases of the— B B V LYON 258
- Liver, The Effects of Chronic Disease
of the—on the Composition and
Physicochemical Properties of Blood
Changes in the Serum Proteins, Re-
duction in the Oxygen Saturation of
the Arterial Blood A M SNIEL 690
- Liver in Hemopoiesis, The Role of the
— *Edit* 992

- Liver Therapy, Intensive—in Sprue
P CORR 1182
- Lobar Pneumonia and Serum Therapy
F T LORD and R HEFFRON *Rev* 1756
- Lung Anatomy and Pathology, Basic
Points in Roentgen-Ray Studies of
— K DUNHAM and J H SKAVLEM 555
- Lung Infections, Accessory Sinus In-
fection, Its Relation to Mastoid and
— W F MANGES 547
- Lymphatic Hyperplasia, Lymphopoiesis,
—and Lymphemia Fundamental Ob-
servations Concerning the Pathologic
Physiology and Interrelationships of
Lymphatic Leukemia, Leukosarcoma
and Lymphosarcoma B K WISE-
MAN 1303
- Lymphatics, Growth and Development
of Function in Blood Vessels and—
E R CLARK 1043
- Lymphedema of the Extremities
Etiology, Classification and Treat-
ment, Report of 300 Cases E V
ALLEN and R K GHORMLEY 516
- Lymphopoiesis, Lymphatic Hyperpla-
sia, and Lymphemia Fundamental
Observations Concerning the Patho-
logic Physiology and Interrelation-
ships of Lymphatic Leukemia, Leu-
kosarcoma and Lymphosarcoma B
K WISEMAN 1303
- M**ECHANISMS of Healing in
Collapse Therapy, The— M
PINNER 501
- Medical Tactics and Logistics G M
BLECH and C LYNCH *Rev* 1440
- Medicine, The Changing Order in—
J A MILLER 1287
- Medicine and Surgery, Fifty Years of
— F H MARTIN *Rev* 642
- Medicine and Surgery, The Practi-
tioner's Library of— Vol VIII
Therapeutics G L BLUMER (Su-
pervising Editor) and A I SULLI-
VAN (Associate Editor) *Rev* 210
- Medicine and Surgery, The Practi-
tioner's Library of— Vol IX
Neurology and Psychiatry G
BLUMER (Supervising Editor) and
J C FOX, JR., and C C FRY (As-
sociate Editors) *Rev* 1268
- Medicine in the Middle Ages, The
Study of— D RIESMAN *Rev* 491
- Meningitis, Tonsillitis Associated with
Acute Aseptic— D RIFSMAN *Case
Rep* 1427
- Meningococcus Infection, Acute Ful-
minating—, with Bilateral Capillary
Hemorrhage of the Adrenals as the
Most Striking Gross Pathologic Le-
sion F H FOUCAR *Case Rep* 1736
- Menstruation, Allergic Coryza at—
from Ovarian Hormone F A
RIEBEL *Case Rep* 91
- Mercuric Chloride Poisoning, The
Treatment of Acute— E HULL and
L A MONTE 54
- Metabolism, Disturbances of the En-
docrine Balance and Their Relation
to Diseases of— C N H LONG 1619
- Metabolism in Hyperthyroidism,
Studies on the Increased— E C
ANDRUS and D McEACHERN 579
- Metabolism of Creatine and Creatinine
in Muscle Disease A T MIL-
HORAT and H G WOLFF 834
- Metabolism Studies in Myasthenia
Gravis before and during the Ad-
ministration of Glycine M ADAMS,
M H POWER and W M BOOTHBY 1330
- Michigan, Notes on Medical Educa-
tion and Medical Institutions in— 1024
- Mouth, Diseases of the—and Their
Treatment H PRINZ and S S
GREENBAUM *Rev* 811
- Mouth Infection O T OSBORNE
Rev 997
- Multiple Sclerosis, Studies in— VIII
Etiologic Factors in Multiple Sclero-
sis T J PUTNAM 854
- Myasthenia Gravis (Sixth Report)
W M BOOTHBY 143
- Myasthenia Gravis, Chemical Studies
in— M ADAMS, M H POWER and
W M BOOTHBY 823
- Myasthenia Gravis, Metabolism
Studies in—before and during the
Administration of Glycine M
ADAMS, M H POWER and W M
BOOTHBY 1330
- Myocardial Insufficiency by Cardiac
Output Methods, Cardiac Output in
Common Clinical Conditions, and the
Diagnosis of— I STARR, JR., and
C J GAMBLE 569
- Myocardium, Report of a Case of Left
Ventricular Failure with Unusual

- Anatomical Changes in the— H ROESLER and L A SOLOFI *Case Rep* 477
- Myxedema, Internal—, Report of a Case Showing Ascites, Cardiac, Intestinal and Bladder Atony, Menorrhagia, Secondary Anemia and Associated Carotinemia R F ESCAMILLA, H LISSER and H C SHILP-ARDSON 297
- N**ARCOLEPSY, The Treatment of—with Benzedrine Sulphate H ULRICH, C E TRAPP and B VIDGOTT 1213
- Nephritis, Prognosis in Acute Glomerular— A B RICHTER 1057
- Nephritis, Terminal Hemorrhagic— A Case Exemplifying the Protean Character of Its Signs and Symptoms I H PAGE *Case Rep* 1419
- Nephritis, The Diagnosis and Treatment of Variations in Blood Pressure and— H O MOSENTHAL *Rev* 1754
- Nervous Patient, The— C P EMERSON *Rev* 353
- Nervous System, Diseases of the— W R BRAIN *Rev* 641
- Neurocirculatory Asthenia Report of a Case Treated by Adrenal Denervation J P ANDERSON *Case Rep* 1255
- Neurological Symptoms in Posthemorrhagic Secondary Anemia S B HADDEN 1572
- Neurology, The Principles and Practice of— A CANNON and E D T HAYES *Rev* 96
- Neurology and Psychiatry Vol IX — The Practitioner's Library of Medicine and Surgery G BLUMFEL (Supervising Editor) and J C FOX, JR and C C FRY (Associate Editors) *Rev* 1268
- Neurosurgery, Practical Neurological Diagnosis, with Special Reference to the Problems of— R G SPURLING *Rev* 1158
- Neutrophilic Index, Effect of Vibratory Stimulation on the— J C HEALY, M H SWEET and F P CHILLINGWORTH 123
- of a Case Due to Carcinomatous Thromboangitis Obliterans of the Thoracic Duct and Upper Great Veins W M YATER 600
- Nucleotides, Therapeutic Action of the —, the Treatment of the Whole Blood Picture with Ferrous Adenylate S L RUSKIN and E KATZ 1549
- O**BITUARIES
- Barnes, Frederick Rigby 497
- Bethel, George E 217
- Bettmann, Henry Wald 1169
- Blair, Alexander McNeil 1021
- Brooks, Harlow 1615
- Brown, George Elgie 1017
- Brundage, Albert Harrison 1618
- Caille, August 817
- Carey, Harry Wardwell 819
- Chalmers, Thomas 1020
- Dexter, Thurston Hopkins 498
- Eckel, John Leonard 1282
- Epplen, Frederick 496
- Goodall, Harry Winfred 495
- Heagey, Francis W 500
- Henderson, Walter Ford 106
- Hinton, Charles Crawford 1286
- Holmes, Arthur D 1761
- Hyndman, Henry Finlay 1283
- Igaravidez, Pedro Gutierrez 818
- Irwin, Stewart Vernon 648
- Jackson, Edward W 1019
- Jennings, Charles Godwin 1167
- Jerman, Louis F 496
- Krauss, William 1284
- Lea, Jessie Worthy 500
- McCaskey, George Washington 1285
- Morris, John Mason 498
- Nahman, Adolph H 821
- Norden, Henry Aaron 104
- Pietrowicz, Stephen R 1285
- Polozker, Isaac Louis 820
- Quntard, Edward 1617
- Reyher, Christopher M 1617
- Roussel, Albert Edward 1022
- Royster, James Hunt 105
- Silver, Lewis Mann 1019
- Simonds, Clarence Eugene 1761
- Smith, Morgan 818
- Smith, Webster Stanley 1762
- Susslin, Emil Joseph 822
- Warnick, John William 218
- Welker, Franklin 499

Oleothorax Clinical and Experimental
J N HAYES 779
Osteomyelitis, Primary Costal— H
R ROEHM *Case Rep* 200
Out-Patient Clinic Problems of Today
Edit 207
Oxygen Treatment and Thyroid Ablation
in the Treatment of Heart Disease
A L BARACH, D W RICHARDS and W B PARSONS 1513

PANCREATIC Lithiasis D B
FAUST *Case Rep* 625

Parathyroid Gland, Adenoma of the—
with Hyperparathyroidism S S
RIVEN and M F MASON *Case Rep* 1578

Paroxysmal Ventricular Tachycardia,
Report of a Case Illustrating All the
Accepted Diagnostic Criteria A E
PARSONNET *Case Rep* 1258

Pediatric Treatment P S POTTER
Rev 997

Peptic Ulcer, Combined Medical and
Surgical Management of—, with
Emphasis on the Treatment of Hemorrhage
J W THOMPSON and H W SOPER 1106

Peptic Ulcer, The Value of a Mixture
of Powdered Milk and Alkali for
Neutralizing the Gastric Acidity of
Patients with— P H WOSIKA and
E S EMERY, JR 1078

Pernicious Anemia with Normal Blood
Picture C H SANFORD 189

Personality and the Endocrines, A
Study Based upon 1400 Quantitative
Necropsies W FREEMAN 444

Philosophers, Three— (Lavoisier,
Priestley and Cavendish) W R
ALKROYD *Rev* 1440

Phosphatase Content of Human Serum
in Pulmonary Tuberculosis Following
the Administration of Vitamin
D P D CRIMM and J W STRAYER 1393

Physical Diagnosis R C CABOT
Rev 1440

Physical Diagnosis W P ELMER
and W D ROSE *Rev* 492

Physical Diagnosis, Principles and
Practice of— P MARTINI *Rev* 642

Pineal Glands, Further Studies on the
Thymus and— L G ROWNTREE,
J H CLARK, A STEINBERG, A M

HANSON, N H EINHORN and W
A SHANNON 359
Pituitary Gland, The Thyroid Stimulating
Hormone of the Anterior—
L LOEB 13
Placental Extracts, Immunological Applications
of—, Effectiveness by Oral Administration
C F MCKHANN, A A GREEN, L E ECKLES and J
A V DAVIES 388
Pneumococcus Type III Pneumonia
Edit 1266
Pneumonia, Abdominal Distention in
Lobar— J GOLDMAN and A COHEN 1222
Pneumonia, Artificial Pneumothorax
in the Treatment of Lobar— B
BURBANK and E ROTHSTEIN 376
Pneumonia, Pneumococcus Type III—
Edit 1266
Pneumonia, The Present Status of
Artificial Pneumothorax in the Treatment
of Lobar— S S LEOPOLD and L M LIEBERMAN 19
Pneumonia, Treatment of—with Serum
Containing Type-Specific, Heterophile,
and Neutralizing Antibodies
V B CALLOMON and J UNGAR 1664
Pneumonokoniosis, Etiology of the
Pulmonary Fibroses and Medical-Legal
Aspects of— W S MCCANN 234
Pneumothorax in the Treatment of
Lobar Pneumonia, Artificial— B
BURBANK and E ROTHSTEIN 376
Pneumothorax in the Treatment of
Lobar Pneumonia, The Present Status
of Artificial— S S LEOPOLD and L M LIEBERMAN 19
Polomyelitis, a Handbook for Physicians
and Medical Students J F LONDON and L W SMITH *Rev* 808
Posture and Blood Pressure *Ldit* 638
Potassium, The Importance of—in the
Treatment of Addison's Disease
Edit 1752
Powdered Milk and Alkali, The Value
of a Mixture of—for Neutralizing
the Gastric Acidity of Patients with
Peptic Ulcer P H WOSIKA and
E S EMERY, JR 1078
Practical Neurological Diagnosis, with
Special Reference to the Problems
of Neurosurgery R G SPURLING
Rev 1158

- Pregnancy, The Etiology and Prevention of Anemia in— M B STRAUSS 38
- Pregnant and Non-Pregnant Females, The Incidence of the Clinical Types of Syphilis in Males, in— W C MENNINGER and J E KEMP 175
- Premature Contractions and Bundle Branch Lesions, Localization of the Site of Experimental—by Means of Mammalian Chest Leads J WRINSLY and I ABRAMSON 1187
- President, American Society J C MERRINS 1
- Primary Costochondritis H R ROEHM *Case Rep* 200
- Primary Tumors of the Heart, with Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis before Death S A SHELburne *Case Rep* 340
- Prognosis in Acute Glomerular Nephritis A B Richter 1057
- Proliferative Intimitis of Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis, and Recurring Necrotic Ulcers of the Skin N W BARKER and T W BAKER *Case Rep* 1134
- Psychiatry, Child— L KANNER *Rev* 211
- Psychiatry, Neurology and— Vol IX — The Practitioner's Library of Medicine and Surgery G BRUMER (Supervising Editor) and J C Fox, Jr and C C Fry (Associate Editors) *Rev* 1268
- Psychiatry, Objective and Experimental— D E CAMERON *Rev* 809
- Psychoneuroses, Some Factors in the Etiology of the— L CASAMAJOR 1677
- Psychopathology, Essentials of— G W HENRY *Rev* 1269
- Psychoses in Pernicious Anemia, Symptomatic— P W PREU and A J GEIGER 766
- Public Health Nursing in Industry V H HODGSON *Rev* 354
- Pulmonary Fibroses, Etiology of the— and Medico-Legal Aspects of Pneumonokoniosis W S McCANN 234
- Pulmonary Fibrosis and Emphysema J A MILLER 219
- Pulmonary Torulosis R M HARDWAY and P M CRAWFORD *Case Rep* 334
- Purpura, Experimental Thrombopenic —, Cytological and Physical Changes in the Blood L M TOCANTINS 838
- Purpura, Thrombopenic— *Edit* 350
- Purpura, Thrombopenic—, An Analysis of 160 Cases W M FOWLER 1475
- R**ADIUM Treatment of Skin Diseases, New Growths Diseases of the Eyes and Tonsils F H WHITMAN *Rev* 996
- Readmissions, A Study of 118—to Oakhurst Sanatorium of Grays Harbor County, Washington H L HULL 134
- Renal Disease, The Interrelationship of Gastrointestinal and— H GAUSS 1373
- Renal Dwarfism J F ROBERTS *Case Rep* 1729
- Renal Failure, Fatal Diabetic Coma with Acute— M E HOLMES 426
- Rheumatic Fever and Rheumatoid Arthritis, Studies Relating Vitamin C Deficiency to—, Experimental, Clinical and General Considerations J F RINFHART I Rheumatic Fever 586 II Rheumatoid (Atrophic) Arthritis 671
- "Rheumatism," The Present Status of the Problem of—and Arthritis, Review of American and English Literature for 1934 P S HENCH, W BAUER, A A FLETCHER, D GHRIST, F HALL and T P WHITE 883
- Roentgenologic Niche in Duodenal Ulcer, Incidence and Significance of the— B R KIRKLIN and H A BURCH 436
- Roentgen-Ray Chest Survey of All Hospital Admissions, The Medical and Economic Advantages of a— F J HODGES 1639
- Roentgen-Ray Studies of Lung Anatomy and Pathology, Basic Points in— K DUNHAM and J H SKAVLEM 555
- Rush, Benjamin,—Physician and Citizen N G GOODMAN *Rev* 1606
- S**CHILLER, the Greatest of the Medical Poets L H RODDIS 1240
- Sclerosis, Studies in Multiple— VIII Etiologic Factors in Multiple Sclerosis T J PUTNAM 854

- Sedimentation Time in Acute Cardiac Infarction C SHOOKHOFF, A H DOUGLAS and M A RABINOWITZ 1101
- Septicemia and Erythema Nodosum, Gonorrheal— H J BAKST, J A FOLEY and M E LAMB *Case Rep* 790
- Serum Therapy, Lobar Pneumonia and — F T LORD and R HEFFRON *Rev* 1756
- Silicosis, The Experimental and Pathological Aspects of— D IRWIN 540
- Sinus Infection, Accessory—, Its Relation to Mastoid and Lung Infections W F MANGES 547
- Sippy Regimen, The Effectiveness of the—in Neutralizing the Gastric Juice of Patients if the Amount of Alkali Is Not Varied P H WOSIKA and E S EMERY, JR 1070
- Skeletal Effects, Diet of the Bluff Dwellers of the Ozark Mountains and Its— E G WAKEFIELD and S C DELLINGER 1412
- Smoking, Excessive—as a Possible Precipitating Factor in Diabetic Gangrene, with a Case Report H BLOTNER *Case Rep* 987
- Sodium Compounds, The Treatment of Addison's Disease with—, with the Report of One Case and the Summaries of Eleven Other Collected Cases Thus Treated E C REIFENSTEIN and E C REIFENSTEIN, JR 1338
- Solitary Ulcer of the Ileum and Ulcer of Meckel's Diverticulum P W BROWN and J DEJ PEMBERTON 1684
- Splenic Vein Thrombosis and Its Relationship to Banti's Syndrome, with Report of a Case H D LEINOFF *Case Rep* 85
- Sprue, Intensive Liver Therapy in— P CORR 1182
- Stomach and Duodenum, The— G B EUSTERMAN and D C BALFOUR *Rev* 1755
- Study of 118 Readmissions to Oakhurst Sanatorium of Grays Harbor County, Washington— H L HULL 134
- Subacute Bacterial Endocarditis of the Aortic Valve Previously Rendered Incompetent by Infarction of the Papillary Muscle and Shortening of the Chordae Tendinae I I LEMANN *Case Rep* 1587
- Surgical Procedures in Essential Hypertension G E BROWN *Edit* 488
- Symptomatic Psychoses in Pernicious Anemia P W PREU and A J GEIGER 766
- Syphilis, Clinical Management of— A R HARNES *Rev* 353
- Syphilis, Hepatic Complications in the Treatment of— II Incidence of Hepatic Disease in Patients with treated Syphilis and during Subsequent Treatment N N EPSTEIN and W J FARR 1561
- Syphilis, The Incidence of the Clinical Types of—in Males, in Pregnant and Non-Pregnant Females W C MENNINGER and J E KEM. 175
- T**HERAPEUTIC Action of the Nucleotides, the Treatment of the Whole Blood Picture with Ferrous Adenylate S L RUSKIN and E KATZ 1549
- Therapeutic Effect of Solution of Potassium Arsenite in Chronic Erythrogenous Leukemia, The— L STEPHENS and J S LAWRENCE 1488
- Therapeutics Vol VIII — The Practitioner's Library of Medicine and Surgery G L BLUMER (Supervising Editor) and A I SULLIVAN (Associate Editor) *Rev* 210
- Thrombopenic Purpura *Edit* 350
- Thrombopenic Purpura, An Analysis of 160 Cases W M FOWLER 1475
- Thrombopenic Purpura, Experimental —, Cytological and Physical Changes in the Blood L M TOCANTINS 838
- Thymus and Pineal Glands, Further Studies on the— L G ROWNTREE, J H CLARK, A STEINBERG, A M HANSON, N H EINHORN and W A SHANNON 359
- Thyroid Ablation, Oxygen Treatment and—in the Treatment of Heart Disease A L BARACH, D W RICHARDS and W B PARSONS 1513
- Thyroid Gland, Diseases of the— A E HERTZLER *Rev* 809
- Thyroid Stimulating Hormone of the Anterior Pituitary Gland, The— L LOEB 13
- Tonsillitis Associated with Acute Aseptic

- tic Meningitis D RIFSMAN *Case Rep* 1427
- Torulosis, Pulmonary— R M HARD-
AWAY and P M CRAWFORD *Case Rep* 234
- Toxic Reaction to Alpha-Dinitro-Ortho-Cresol M B GORDON and M J WALLFIELD 198
- Trachea, The Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larynx and— A L BARACH 739
- Treatment of Chronic Rheumatoid Arthritis, Further Observations on the Use of Streptococcal Vaccine C W WAINWRIGHT 245
- Treatment of Peripheral Vascular Disease by Means of Suction and Pressure E M LANDIS and L T HITZROT 264
- Tuberculosis, Factors in the Falling Death Rate from— *Edit* 1154
- Tuberculosis, Gynecological and Obstetrical— E M JAMESON *Rev* 997
- Tuberculosis Following the Administration of Vitamin D, Phosphatase Content of Human Serum in Pulmonary— P D CRIMM and J W STRAYER 1393
- ULCER, Solitary—of the Ileum and Ulcer of Meckel's Diverticulum P W BROWN and J DEJ PEMBERTON 1684
- Undulant Fever, Intermittent Hydrarthrosis Associated with— J C SHARPE *Case Rep* 1431
- VACCINE, Treatment of Chronic Rheumatoid Arthritis, Further Observations on the Use of Streptococcal— C W WAINWRIGHT 245
- Vascular Disease, Treatment of Peripheral—by Means of Suction and Pressure E M LANDIS and L T HITZROT
- Vascular Disease in the Obese Diabetic, and in Non-Diabetics, A Discussion of Arteriosclerosis as a Cause of Diabetes E C BECK, J G FOWLER, E C KOENIG and B D BOWEN
- Ventricular Complexes of the Bundle-Branch-Block Type Associated with Short P-R Intervals G H ROBERTS and D I ABRAMSON *Case Rep*
- Vibratory Stimulation on the Neutrophilic Index, Effect of— J C HRALEY, M H SWEET and F P CHILLINGWORTH
- Viruses and the Diseases Caused by Them T M RIVERS
- Vitamin C Deficiency, Studies Relating—to Rheumatic Fever and Rheumatoid Arthritis, Experimental, Clinical, and General Considerations J F RINEHART
I Rheumatic Fever
II Rheumatoid (Atrophic) Arthritis
- Vitamin D, Phosphatase Content of Human Serum in Pulmonary Tuberculosis Following the Administration of— P D CRIMM and J W STRAYER
- Von Gierke's Glycogen Disease L M LINDSAY, A ROSS and F W WIGGLESWORTH
- WATER, The Movement and Distribution of Body— *Edit*

